UNITED STATES OF AMERICA

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FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANESTHETIC AND LIFE SUPPORT DRUGS ADVISORY COMMITTEE

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MEETING

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WEDNESDAY

SEPTEMBER 17, 1997

The Committee met in the Grand Ballroom of the Gaithersburg Hilton Hotel, 620 Perry Parkway , Gaithersburg, Maryland, at 8:0 0 a.m., Dr. John Downs, Chairman of the Committee, presiding.

PRESENT:

DR. JOHN G. DOWNS	A LSAC Chairman
MARY G. CURLL	ALSAC
DR. JOHN E. ELLIS	ALSAC
DR. SUSAN K. PALMER	ALSAC
DR. MARGARET WOOD	ALSAC
DR. MARIE YOUNG	ALSAC
DR. CHARLES ROHDE	ALSAC
DR. JOHN J. SAVARESE	ALSAC

DR. AMANDA S. CARLISLE	ALSAC	
DR. TERESE HORLOCKER	ALSAC	
DR. EDWARD LOWENSTEIN	ALSAC	
DR. MEHERNOOA F. WATCHA	ALSAC	
DR. HARRIET DE WIT	DAAC	
DR. LAURA F. McNICHOLAS	DAAC	
DR. DEREK RAGHAVAN	ODAC	
SUZANNE BROWN	SGE	
DR. PETER ROTHSTEIN	SGE	
DR. RONNY HERTZ	SGE	
DR. MITCHELL MAX	SGE	
DR. ERIC STRAIN	DAAC	
DR. KATHLEEN FOLEY	Guest Expert	

ALSO PRESENT:

DR. CYNTHIA McCORMICK	FDA	
DR. CURTIS WRIGHT	FDA	
DR. SURESH DODDAPANENI	FDA	
DR. ROBERTA KAHN	FDA	
DR. MICHAEL KLEIN	FDA	
DR. KAREN THEMPLETON-SOMERS	ALSAC	Exec. Secy.
DR. STEPHEN SHOEMAKER	ANESTA	
DR. RUSSELL K. PORTENOY	ANESTA	
DR. CLAIR CALLAN	Abbott Labs.	

C O N T E N T S

P R O C E E D I N G S

8:03 a.m.

CHAIRMAN DOWNS: We obviously have a very full agenda this morning so I'd like to try stick to the schedule as much as possible. And to begin with, if we could please go around the table to introduce everyone at the main table. Dr. McCormick, would you begin, please?

DR. McCORMICK: Hello, I'm Dr. Cynthia McCormick. I'm the Director of the Division of Anesthetics, Critic Care, and Addiction Drug Products, FDA.

CHAIRMAN DOWNS: I'd like to also have everyone speak into the microphone so the transcriptionist can get the record.

DR. WRIGHT: Dr. Curtis Wright, Deputy Director of the Division.

DR. KAHN: Good morning. Dr. Roberta Kahn, Medical Officer.

DR. YOUNG: Dr. Marie Young, University of Pennsylvania.

DR. SAVARESE: Dr. John Savarese, Cornell University.

DR. PALMER: Dr. Susan Palmer, University of Colorado Health Sciences Center.

DR. ELLIS: Dr. John Ellis, University of Chicago.

DR. WOOD: Dr. Margaret Wood, Columbia University in New York.

MS. CURLL: Mary Gomez Curll, San Antonio, Texas, San Antonio College, Department of Nursing Education.

DR. HORLOCKER: Dr. Terese Horlocker, Mayo Clinic, Rochester, Minnesota.

DR. SOMERS: Karen Somers, Executive Secretary for the Committee.

DR. DOWNS: Dr. John Downs from the University of South Florida in Tampa.

DR. CARLISLE: I'm Dr. Sue Carlisle from the University of California, San Francisco.

DR. WATCHA: Dr. Meh Watcha, University of Texas, Southwestern Medical Center.

DR. ROHDE: Chuck Rohde, Department of Biostatistics at Johns Hopkins University.

MS. BROWN: Suzanne Brown from Portland, Oregon.

DR. ROTHSTEIN: Dr. Peter Rothstein, Columbia University.

DR. MAX: Dr. Mitchell Max, Pain Research Clinic, National Institute of Dental Research.

DR. HERTZ: Ron Hertz, St. Luke's Roosevelt Hospital, New York City.

DR. McNICHOLAS: Dr. Laura McNicholas, University of Pennsylvania and the VA.

DR. RAGHAVAN: Derek Raghavan, University of Southern California, from the Oncology Drug Advisory Committee.

DR. de WIT: I'm Harriet de Wit from the University of Chicago and the Drug Abuse Advisory Committee.

DR. STRAIN: I'm Eric Strain from Department of Psychiatry, Johns Hopkins, and I'm on the Drug Abuse Advisory Committee.

CHAIRMAN DOWNS: Thank you very much. May I have the Conflict of Interest Statement read by Dr. Somers?

DR. SOMERS: The following announcement addresses the issue of Conflict of Interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interest in firms regulated by the Center for Drug

Evaluation and Research present no potential for an appearance of conflict of interest at this meeting with the following exceptions.

We would like to disclose for the record that Dr. Terese Horlocker's employer, the Mayo Clinic, has in interest which does not constitute a financial interest within the meaning of 18 U.S.C. 208(a), but which could create the appearance of a conflict.

The agency has determined, notwithstanding this involvement, that the interests of the government and Dr. Horlocker's participation outweighs the concern that the integrity of the agency's programs and operations may be questioned. Therefore, Dr. Horlocker may participate in all official matters concerning *Actiq*™.

We would also like to disclose for the record that one of Dr. Eric Strain's colleagues at the Johns Hopkins Bay View Medical Center is attending the meeting today as a consultant to Anesta.

The agency has determined, notwithstanding this association, that the interests of the government and Dr. Strain's participation outweighs the concern that the integrity of the agency's programs and operations may be questioned. Therefore, Dr. Strain may participate in all official matters concerning

Anesta's *Actiq*™ but without voting privileges.

In addition, we would like to disclose for the record that Dr. John Ellis' employer, the University of Chicago, participated in several studies concerning Anesta's Oral Transmucosal Fentanyl Citrate. Since Dr. Ellis had no involvement whatsoever in these studies, he may participate in all official matters concerning *Actiq*™.

With respect to FDA's invited guest expert, Dr. Kathleen Foley, she's reported interests which we believe should be made public to allow the participants to objectively evaluate her comments. Dr. Foley would like to disclose for the record that she has received grants from Purdue Frederick, Knoll, and Janssen.

Dr. Foley's institution, the Memorial Sloan-Kettering Cancer Center, studies OTFC but she was not the principal investigator. She has received consulting fees and honoraria from all of the companies over the years that are involved in cancer pain management.

She has also received honoraria for talks on pain medicine and opioid use from all of the companies. Additionally, Dr. Foley is a member of the U.S. Cancer Relief Committee and project director of

the project on Death in America.

In the event the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness, that they address any current or previous financial involvement with any firm whose products they may wish to comment upon. Thank you.

DR. WATCHA: Mr. Chairman, for the sake of the record, Meh Watcha, the University of Texas has received -- of which I am a member -- has received some grants for the study of OTFC in the past. I have not been a principal investigator for that particular one. I've also received a grant for a study by Abbott Labs for OTFC three years ago.

CHAIRMAN DOWNS: Dr. McCormick. Would you like to make some opening remarks for the FDA please? Oh, I'm sorry, I sort of jumped ahead, didn't I? I apologize. We would have moved along very efficiently if we had begun that way.

The open public hearing speakers as I have

listed is, Carol Curtiss will be the first speaker.

MS. CURTISS: Good morning. I'm Carol Curtiss. I'm an Oncology Clinical Nurse Specialist in private practice, past President of the Oncology Nursing Society, and Volunteer locally and nationally for the American Cancer Society.

I'm a founding member of the Massachusetts Cancer Pain Initiative, and currently represent the Oncology Nursing Society as a member of the United States Committee International Union Against Cancer.

I graduated from the Massachusetts General Hospital and hold a master's degree in Oncology Nursing from Yale University. At this meeting I'm speaking as an individual, however. I do not have a financial interest in Anesta Corporation but I have been asked to participate in the future in Professional Education Speaker's Bureau for the corporation.

I have no firsthand, clinical experience with *Actiq*™. I do have nearly 20 years experience managing cancer pain, though. I've presented educational programs in 41 states and nine countries. I paid my own way to attend this meeting because I'm committed to improving the way we manage cancer pain. Clinically, I've seen firsthand the horror and the

suffering that accompanies unrelieved pain, and have dedicated my professional life to improving things.

I think it's fair to say that everyone in this room either has been or will be, affected by cancer and cancer pain. For those of you who are lucky, your memories will be good ones, of loved ones who lived life to its fullest because of adequate pain relief. For the rest of us, our memories will be of needless pain and suffering, and those memories live on in families who survive.

Pain is often more frightening to people with cancer than death itself. I can't tell you how many times in my practice that individuals have said to me, it's not the dying that bothers me; I'm afraid I won't be able to deal with the pain. Or if you could just get rid of this pain I could go back to work and have a life that's fulfilling.

While most cancer pain can be relieved by rather easy methods, we continue to have needless suffering. Clinical studies continue to show that pain is poorly relieved, patients are undermedicated, and the burden of care has been shifted to patients and families at home. Patients and families are often reluctant to take medicines at all.

Changes in our health care system further

complicate the problem, shifting care from healt h professionals again to patients and families. Home i s now the primary place of care for most people wit h cancer at all stages of illnes s. Who would have ever thought that bone marrow transplant would be largely an outpatient procedure?

Therapy that would have once been unde r close scrutiny of an inpatient setting is no w relegated to patients and fami lies. In my experience and that of nurses from around this country, patients and families assume this care extraordinarily well.

It's important to note that we already have strong medications in the home. Meds like Morphine, Oxycodone, Hydromorphone, and Fentanyl, titrated t o patien t comfort. We entrust families with long an d short acting oral medicines in multiple dosin g strengths and instruct them to adjust doses, sometime s daily or more often.

We ask them to provide primary an d supportive care for infusion pumps, epidural an d interthecal catheters, and other technology, and t o remember change patches, often multiple, every two to three days. It's important to note too, that in m y State, nurses are not allowed to inject medicines int o spinal catheters, yet patients and families ar e

required to do this at home all the time.

Yet in my experience and that of others, patients and families act responsibly and very cautiously, as they manage pain. In practice, they're pretty stingy with their medicines, often taking far less than what physicians prescribe. When a loved one dies, one of the first calls is often, please come get this medicine; I don't want it around my house.

In all of my years of practice following patients in ambulatory home and hospice settings, I have found patients and families are very concerned and very careful with safe handling, and extremely conservative about their strong medicines.

In your deliberations, in conclusion I ask that you consider the following. Unrelieved cancer pain has a profound impact on patients and families, and increases needless suffering and increases the burden of care.

Currently, many Class 2 analgesics in a variety of forms, in a wide range of titrated doses, are already used safely at home. Patients adjust oral doses, change patches, and even sometimes reprogram infusion pumps with only written instructions or a telephone call from a health provider.

Please consider the importance of providing

an additional option for effective cancer pain relief, especially breakthrough pain, and its ability to help clinicians manage pain better. In the person with cancer, the right doses is the dose that works, and may vary dramatically from person to person.

Our goals for effective pain management are the best relief with the fewest side effects, with the least invasive, easiest plan to follow. When patients have options for effective pain management they gain greater control over their lives.

Effective pain relief is the cornerstone of improving quality of care for individuals with cancer. Having a variety of medications to manage persistent and breakthrough pain that can be adjusted to individual response, are proven keys to our success. At your places you have a fact sheet that I've prepared with some of the studies that support the information I've just given you. Thank you.

CHAIRMAN DOWNS: Thank you. Dr. Sharon Weinstein.

DR. WEINSTEIN: Good morning. If I may distribute the outline. Thank you for this opportunity to speak with you this morning. My professional affiliation is with University of Texas and the Anderson Cancer Center, however, I am speaking

on behalf of the American Alliance of Cancer Pain Initiatives this morning.

The Alliance of Cancer Pain Initiatives is a group of non-profit, voluntary organizations of lay public and professionals. Over the past ten years State-level organizations have developed with increasing recognition of the problem of undertreatment of cancer pain.

Reasons for the undertreatment of cancer pain have been well-documented, including the lack of access to opioid analgesics which are safe and effective drugs. Undertreatment has also been attributed to excessive public and professional fear of addiction and the over-emphasis of other possible but rare adverse effects, such as respiratory depression.

Morphine and Morphine-like drugs have an associated stigma which continues to impede the management of cancer pain. The Cancer Pain Initiatives have therefore stepped up their efforts, and we now have a national alliance because the problem is not solved. Unrelieved pain has high costs including patients' withdrawal from potentially life-saving cancer treatment and even suicide.

The World Health Organization and many

national professional organizations have physician statements that the management of pain should be a high priority in the care of cancer patients regardless of the state of their disease. The mission of the Cancer Pain Initiatives then, is to achieve control of cancer pain.

In terms of the prevalence, cancer pain is related to actual disease and its treatments. Worsening pain usually occurs in the setting of progressive disease. Chronic, severe pain may also persist long after successful cancer treatment as a result of chemotherapy, radiotherapy, or surgery. In children with cancer, pain is often associated with medical procedures.

Based on the prevalence of cancer and cancer-related pain, a conservative estimate of the number of Americans requiring opioids for their cancer pain at this time would be excess of one million persons.

The World Health Organization's 3-step analgesic ladder, a titration protocol for the pharmacotherapy of cancer pain, has been validated in international studies showing that 75 to 90 percent of cancer patients can obtain adequate relief of pain using opioids in combination with other drugs, usually

through the oral route of administration.

Our own agency for health care policy and research released comprehensive guidelines for the management of cancer pain in 1994. It is emphasized that inter-individual response to opioid analgesics is quite variable, and that doses must be adjusted according to the patient response.

Following these standard guidelines on encounters in clinical practice, some patients who require high dose opioids for pain control -- that is, the equivalent of grams of parenteral Morphine on a daily basis. Patients are maintained as outpatients with a variety of analgesic techniques, including parenteral infusions of high dose opioids with a patient-controlled analgesia feature for self-administration of intravenous, subcutaneous, and even spinal boluses.

There are several clinical situations in which the titration of oral medication is not feasible or successful. Some patients are not able to swallow pills, especially not in large quantities. Some patients may have lower gut obstruction, with or without draining gastrointestinal tubes.

Incident pain which is due to a particular movement or activity is difficult to control with

analgesic formulations that are meant to provide sustained, analgesic blood levels over an extended period of time. This type of pain, incident pain, is often associated with bony metastases which are the most common, painful complication of cancer.

Spontaneous pain such as unpredictable neuropathic pain, is also very difficult to control for the same reasons, and is often relatively brief but very severe in intensity. Neuropathic pain syndromes are also common in cancer.

Finally, there are some patients who are prone to develop side effects on opioids but who will tolerate one drug much better than all others, with an adequate therapeutic ratio of efficacy to side effects obtained with only that one drug.

There are numerous factors which explain why different patients respond differently to the different opioids, or the interesting phenomenon of opioid responsiveness. In terms of pain physiology, we are learning more about the different mechanisms of pain, both opioid and non-opioid, that underlie the clinical syndromes.

The temporal features of different pains would be treated best by drug formulations that have matching pharmacokinetic and pharmacodynamic profiles.

Experienced pain practitioners recently discussed the technique of opioid rotation; that is, intermittently changing the opioid agent in order to reduce total dose and maintain analgesia.

This strategy is based on the understanding that cross-tolerance is incomplete between the different opioid drugs, theoretically due to their different opioid receptor binding profiles. There is preliminary evidence that gender and ethnicity may also affect opioid responsiveness.

And finally, the opioids available for exogenous administration are not chemically identical and drug selective effects may also account for variation and patient responses.

In conclusion, over the past few decades, our therapeutic armamentaria has expanded to better meet the needs of patients. Millions of patients worldwide have been treated with strong opioids in their homes using many different opioid agents through several different routes of administration.

This massive clinical experience has demonstrated that under proper medical supervision cancer patients can be effectively and safely managed with opioids at home.

However, there remain several common

clinical problems for which new formulations of opioids would be very useful and which would enhance our ability to reach our ultimate goals of providing every cancer patient with excellent analgesia and the best quality of life possible.

Thank you. I'm sorry, I -- yes. The expenses for this trip have been paid by Anesta Corporation, but I have received no honoraria, and although there were trials conducted at the University of Texas and the Anderson Cancer Center, I was not a participant in those clinical trials. Thank you.

CHAIRMAN DOWNS: Thank you. Next, Dr. Mary Simmonds.

DR. SIMMONDS: Good morning. Dr. Downs, members of the committee, I am Dr. Mary Simmonds, a practicing medical oncologist. I have been a clinical investigator with *Actiq*™. Today however, I'm representing the American Cancer Society as chair of the National Advisory Group on Cancer Pain Relief.

I am here to speak as an advocate for the many thousands of persons who suffer from cancer and experience pain from this illness. Pain is the most common symptom of this disease, and if the disease progresses, up to 90 percent of persons will experience pain.

If pain is present, it also impacts on sleep, mood, appetite, activity level, and interpersonal relationships; in short, into every aspect of a person's life.

Cancer-related pain is complicated. Often there is more than one site of pain and there may be more than one pain syndrome; that is, a person may suffer neuropathic pain involving a nerve plexus and also somatic pain from bony metastases. There may be more than one etiology of pain including non-malignant pain.

There may be acute pain -- that is, of an incision or pathologic fracture -- but most pain is chronic and unrelenting. Many persons suffer both background or persistent pain and episodic or breakthrough pain. It is therefore a challenge to achieve adequate pain relief so that a person can function as well as possible, particularly if his or her days are foreshortened by this disease.

It will never be easy enough. It is very important to find better ways to more effectively and more conveniently help persons control their pain. The development of Oral Transmucosal Fentanyl Citrate is an important advance, specifically to be able to control the sudden episodes of breakthrough pain.

Breakthrough pain is an important clinical problem. Currently there is no comparable product without a needle.

The American Cancer Society is the nationwide community-based volunteer health organization dedicated to eliminating cancer as a major health problem by preventing cancer, saving lives, and diminishing suffering from cancer through research, education, advocacy, and service.

In closing, I will state that the American Cancer Society not only advocates better ways to relieve cancer pain but also plans to help in educating patients and professionals in the proper use of this new tool so that it will be used properly and safely.

Thank you for this opportunity to speak today.

CHAIRMAN DOWNS: Dr. Simmonds, for the record, do you have any financial association with Abbott or Anesta?

DR. SIMMONDS: As a clinical investigator I received the funds to do the study. Today, I have no financial support whatsoever.

CHAIRMAN DOWNS: Thank you. Next, Mr. Jacob Sitlinger.

MR. SITLINGER: Good morning. My name is Jacob Sitlinger. In April 1986 I was diagnosed with non-Hodgkin's lymphoma. On July 5th, 1986, I began a very intensive chemotherapy series which consisted of 12 treatments of drugs that were injected into the veins and six spinal treatments. I experienced the usual hair loss but also endured many other side effects such as nausea, blistering, and the loss of my finger and toenails. I also was ulcerated in the mouth and throat and was unable to eat due to this ulceration.

The cancer then went into remission until 1989. At that time I was treated orally with cytoxin and again put into remission until 1991 -- and again was treated was cytoxin. In March 1994, I developed an intense pain on my left side that extended from the bottom of my ribs down into my left testicle and into the rectum, into the tips of my toes.

On a scale of one to ten, this pain far exceeded a ten. I would pound on the walls in frustration in attempting to overcome the pain. Tylenol 3 with codeine was giving me little relief and an electrical stimulator was inserted into my spine. The highest setting provided no relief and seemed to make it worse. After four days it was removed.

Many different drugs for the pain were used such as Percocet and Duragesic patches, neither of which provided much relief. The Duragesic patches therapy which were used from December 19th, 1994, until July 19th, 1995, started with 25 milligram patches and ended with two 50-milligram patches.

On July 19th, 1995, I started to use MS Cotin, beginning with 240 milligrams a day which was increased to 720 milligrams a day by June of 1996. During this period I was basically homebound. The pain was affecting me physically, mentally, and emotionally. While I was hospitalized to determine if I can endure and get some relief through the Morphine drip, Dr. Mary Simmonds asked me if I would be willing to try the OTFCs.

In October 1995 I started to use the OTFCs for breakthrough pain. With the MS Cotin and the OTFCs I finally was getting relief, but due to the amount of the MS Cotin I was taking and the side effects, I was referred to Dr. Peter Stotz at the Johns Hopkins Hospital Pain Clinic.

He suggested I try a nerve block. This was done on February the 22nd, 1996. Initially it seemed to help, but did not. A second nerve block was performed with no relief. On June 3, 1996, a

medtronic pump was implanted and after a period of adjustment, the pain that was a ten was reduced to a four and a five, and with the OTFCs, the breakthrough pain was reduced to a two almost immediately.

I felt like I had a life again. I could mow the lawn, do vehicle maintenance, home and appliance repair, plant flowers and shrubs, and I had the desire to go places and to be a better human being. To my family, a great benefit of the OTFCs beside breakthrough pain, was the ease of taking them -- whenever, wherever treatment of breakthrough pain was required I had them.

The OTFCs gave my wife and I some freedom to live our lives that we were missing. I felt that if the OTFCs were more readily available for home use but kept out of the reach of children as all medicines should be, that people who experience severe pain would be given a chance at a better life.

I thank the committee for allowing me to relate the benefits I have received from the use of the OTFCs. To me they were a Godsend. The only financial assistance I have received from the company was lodging last night and a meal. Thank you.

CHAIRMAN DOWNS: Thank you, Mr. Sitlinger. Mr. Anthony Mercantino.

MR. MERCANTINO: Good morning, ladies and gentlemen and thank you very much for giving me this opportunity to come to speak with you. I, as the gentleman before me, am a cancer survivor. I was diagnosed in May of 1988.

My main cancer started off as a prostate cancer, and in about a year-and-a-half metastasized to my spine, and more recently, about a year-and-a-half, up into my skull. And one of the tumors did affect however the muscles work in the head and affected my vision.

I am here because I feel that we all had an opportunity to attack as my pin says, Partners in Pain, to attack this terrible aspect of our disease. When I was diagnosed I didn't realize anything about the pain aspects; you just think about the cancer. But later on the pain certainly makes itself evident, and I guess people think this is the way it has to be.

I've been treated since May of 1988 at Sloan-Kettering Memorial, and I must say the Pain Department recently -- one of the doctors is here today -- had made it very evident to me that I did not have to be in pain and my quality of life could go on.

And as the gentleman said, once we're able to attack the pain and get some control, then we can

do some of the things that all of us are used to doing, like mowing the lawn, and in my case, I like to wash and wax my car instead of paying somebody else to do it. And I was a school administrator for 16 years and it was good to be able to get back as a consultant working with the school.

So I must say, the quality of life was important. And this OTFC is really a Godsend. It worked -- not that one becomes dependent on it. It's just something that you know is going to be effective and it was, and it certainly increased my quality of life. To think back a year-and-a-half ago, I wasn't able to get out of bed and now I'm walking up to four and five miles a day and I feel like a useful citizen, and psychologically, and that's terrific, too.

I want to thank you all for the opportunity. I think as the other survivor said, it really is like any other medication, you would take some care about the house with it, and I just developed a little system where I carry all medications in a little shaving hit and I put it away when we have our grandchildren come and visit. So you just control it. There's really no problem with that aspect of it.

And it certainly is good to know it is there. I thank you all again. I'm here of my

request. The only remuneration was the room, paid by Anesta. I thank you, again.

CHAIRMAN DOWNS: Thank you, Mr. Mercantino. According to the agenda we have no other speakers for the public session. Yes sir? Did you have something further to add? Okay.

Are there any other speakers at this time for the open public session? There will be another session this afternoon.

Seeing none then, we will move on now to the FDA opening remarks and introduction by Dr. McCormick.

DR. McCORMICK: Good morning and welcome to the Anesthetic and Life Support Drugs Advisory Committee. We're meeting today in a public forum to discuss the application for *Actiq*™, Oral Transmucosal Fentanyl Citrate, to hear the concerns of the public on this issue and to ask our advisors to render an opinion that might assist the FDA in reaching a final decision regarding the marketing of this product.

There are special concerns regarding this product which we hope to get on the table for discussion. The palliative treatment of cancer involves the treatment of pain, an area that deserves special attention as the one in which patients are not adequately treated, even after they have reached high

doses of maintenance opiates and who have breakthrough pain.

We've heard the stories and pleas from a number of cancer sufferers and their advocates about how good agents are needed. The product that will be under consideration of this Advisory Committee today is proposed for such a need: Oral Transmucosal Fentanyl Citrate, a potent, synthetic, opioid, analgesic agent in the form of a lozenge on a stick.

We are mindful that the cancer treatment community is strongly in favor of the development of new products for the breakthrough pain where current treatment is not sufficient or simply too slow to provide relief. This product has the advantage over other available treatments in its rapidity of onset.

The FDA will soon be nearing the completion of its review of this product. In support of the indication for cancer breakthrough pain, the sponsor has submitted: one adequate and well-controlled study; two open label titration studies to explore dosing titration schemes; an open label study to evaluate the safety profile of long-term use; four additional control studies exploring use in the non-opioid-tolerant, post-operative population. However, the sponsor has chosen not to market this product in post-

operative pain.

The pivotal study in this product's development used an enrichment design where patients where titrated to a dose which both provided relief and was also tolerated. Not all patients achieved such a dose. Those who did, approximately 70 percent, then entered a double-blind phase where their dose was compared to a placebo. They received a series of OTFC unit does or placebos in a ratio of 7:3 given randomly.

In this study, pain intensity and pain relief were evaluated as endpoints. Doses studied ranged from 200 to 1600 micrograms given at the onset of an episode of pain during the double-blind phase. Rescue medication could be given at 30 minutes if there was insufficient relief.

The pain intensity difference and pain relief from the beginning of an episode to each of 15-minute increments into a final time of 60 minutes, were compared between placebo and treatment. An unquestionable placebo response was seen in both measures, however, the difference between treatment and placebo was statistically significant at all timepoints.

These differences will be examined, I

presume, in the sponsor's and certainly in the FDA's presentations. The Advisory Committee is asked to consider the magnitude of clinical effect demonstrated in the study.

In this, as in the two, open, tolerability studies where titration to a self-selected dose was the goal, there was no clearly identifiable dose or consistent titration scheme. A titration process was purposely not codified during these studies in an effort to simulate the individualized titration that would occur in the hands of a specialist in cancer pain treatment.

The titration then varied with each patient. And how each patient reached the optimum dose ultimately shown to be effective in this study, was not well described. This leaves a void in our ability to develop labeling or to determine how many units might potentially be prescribed for titration to this optimum dose.

The final evaluation of safety in this population is not expected to bring any surprises. The sponsor's evaluation of the safety of this product has included exposure of a total of 517 subjects: of whom 48 were healthy volunteers, 212 were healthy post-operative patients, and 257 were adult opioid-

dependent cancer patients.

Patients in cancer pain trial were treated from one day to over six months. There were 20 in that category. The maximum, single dose per episode that was used in the trials was 7200 micrograms. The safety profile of the drug in cancer pain trials will be discussed, the safety profile in the opiate naive population will also be discussed as this is also relevant to the approval of this product.

Of great importance to the FDA, if in the final analysis this product is determined to be safe and effective in the conditions for proposed use, were those conditions adequate described, is the management of potential public risk in the marketing of this potent narcotic in a form than can be mistaken for candy.

The issues of risk management which may include packaging, labeling, disposal, and possibly restriction, must be fully and adequate addressed by the sponsor before any risk-to-benefit ratio can be determined.

This is a unique situation in which the population that is potentially at the greatest risk of adverse effects, is dissociated from the population that stands to benefit from its approval.

In summary, clearly, patients suffering from cancer pain deserve effective medications -- better than what they currently have -- and the public also deserves to have safe medications. The Advisory Committee can help us to decide whether this proposal in its totality is sufficient to prevent childhood deaths from accidental ingestion, of if there might be an alternative approach that could be considered.

In looking at risk, much of our attention must focus on the non-opioid-tolerant population. To fail to do so would be to ignore the greatest potential for harm.

The FDA will be asking the Advisory Committee to consider the following question: Does the expected benefit to the intended clinical population outweigh the risk of accidental injury inherent in this product, or are there any measures that could be taken that might lessen this risk?

We look forward to a complete and open discussion of these issues. Thank you.

CHAIRMAN DOWNS: Thank you, Dr. McCormick. We'll move on to the sponsor's presentation, then.

DR. SHOEMAKER: If I could have the first slide, please. Dr. Downs and members of the Advisory Committee, Dr. McCormick and other members of the FDA,

I'd like to thank you for the opportunity today to discuss *Actiq*™, or Oral Transmucosal Fentanyl Citrate, which we have studied extensively for the treatment of breakthrough pain and outpatients with cancer.

My name is Dr. Steve Shoemaker and I'm Vice President of Medical Communications at Anesta Corp., and I was the medical director for these cancer pain trails.

Today we're going to discuss several, important, key issues, not the least of which is the treatment or management of breakthrough pain which clearly represents a large, unmet, medical need.

We will describe the clinical program with *Actiq*™ which demonstrates that *Actiq*™ or OTFC, safely and effectively treats breakthrough pain in outpatients with cancer; and we'll also describe how *Actiq*™ is appropriately configured and labeled to provide the adequate safeguards which are necessary when this type of product is introduced into an outpatient environment.

Our presentation will be divided into several parts starting with some background information on OTFC and the specific *Actiq*™ indication. This will be followed by a discussion of

the *Actiq*™ clinical program by Dr. Russell Portenoy who's currently Chairman of Department of Pain Medicine and Palliative Care at Beth Israel Medical Center in New York.

We will then finish the clinical discussion with an integrated summary of safety and this will be followed by a discussion of the risk management program for *Actiq*™ by Dr. Clair Callan, who is Vice President of Medical, Regulatory Affairs and Advanced Research in the Hospital Products Division of Abbott Laboratories.

Now today you'll be hearing from people both from Anesta Corp. and from Abbott, and I'd like to just explain the partnership agreement that we have. Anesta is the NDA sponsor for this product. We were responsible for designing, running, and interpreting clinical trial data.

Abbott Laboratories is a contract manufacturer. They not only manufacture marketed products, but also the products used in clinical trials, and Abbott is also responsible for marketing, sales, and distribution of *Actiq*™.

Our proposed indication then, is for the management of chronic pain, particularly breakthrough pain, in patients already receiving and who are

tolerant to, opioid therapy.

Well, what do we mean by break through pain? Breakthrough pain is defined as a transient flare in pain rising to moderate to severe intensity, that occurs in conjunction with otherwise controlled, persistent pain of moderate or mild intensity.

This is a schematic representation then, of the two components of chronic pain or cancer pain. Patients often have pain that is present day in and day out most of the time; persistent pain. And this persistent pain is often well-managed with the use of controlled released opioids which are dosed on an around-the-clock basis.

Breakthrough pain then, consists of these squares of pain which break through this otherwise adequate level of analgesia. Breakthrough pain characteristically has a sudden onset, by definition is severe, and often has a relatively short duration. Breakthrough pain may occur spontaneously, or it may be related to a specific activity such as movement or walking.

When breakthrough pain is not well managed it can have a very adverse effect on a patient's life. For example, patients with incident pain find that they have to decrease their activity level in order to

prevent pain.

Well, how do we manage breakthrough pain? Well, one approach is merely by increasing the dose of the around-the-clock medication. The problem with this approach is it often leads to overmedication. Patients may complain of too groggy or overly sedated.

An alternative approach is to use a supplemental medication to treat these flares of breakthrough pain, and as pointed out, an ideal medication would have attributes which tend to mask the characteristics of breakthrough pain. In other words, a rapid onset of pain relief, the medication would be potent, and it would have a relatively short duration.

And has also been pointed out previously, some of the limitations of the currently available oral medications is the fact that they have a relatively slow onset.

So for example, one patient in our clinical trials would describe how, when she went out to dinner and would get an episode of breakthrough pain, she would often have to go into the bathroom and lie on the floor for 30 minutes until her oral medications took effect.

Now, waiting 15 to 30 minutes may not seem

like that long, unless you're the patient with severe pain.

Now, we can approach this ideal breakthrough medication more easily in an inpatient environment where patients have access, for example, to IV, PCA, Morphine or other potent opioids. But the use of IV PCA techniques is not practical for many of our outpatients with cancer, and multiple agencies, including the AHCPR and also the ASA which recently released guidelines on the treatment of cancer pain suggests that whenever possible patients should be treated with non-invasive, delivery forms.

Well, the management of breakthrough pain and the problems that we see are more reflective of the general undertreatment of cancer pain. Unfortunately, cancer pain is highly prevalent: 30 percent of patients under active, anti-cancer therapy experience moderate to severe pain; and up to 65 to 85 percent of patients with advanced disease experience pain.

Now, there are multiple barriers to effective cancer pain management. One has been the lack of controlled clinical trials. Although there has been a lot of effort to develop new ways to manage persistent pain -- for example, sustained released

medications of Morphine or oxycodone or transdermal preparations of Fentanyl -- until recently there's been very little work on developing new methods to treat breakthrough pain.

There's inadequate medical training; there's exaggerated fears about the use of opioids, both in clinicians and in patients. And finally, there's a heterogeneity of cancer pain itself. Each patient experienced cancer pain in a unique way, which also points out the importance of developing individualized therapy.

Our approach to managing breakthrough pain has been to consider the use of *Actiq*™, or Oral Transmucosal Fentanyl Citrate which consists of a solid drug matrix containing the potent opioid Fentanyl which is attached to a handle. Now, this handle is clearly marked with an R_x and with the dose of strength, which identifies this unit then, as a serious, medicinal product.

When this unit is placed into the mouth the matrix dissolves, and Fentanyl is rapidly absorbed across the oral mucosa. The oral mucosa is 20 times more permeable than skin and is very well vascularized, which facilitates this rapid absorption. Which means that with OTFC we get the rapid onset of

analgesia in a non-invasive, controllable delivery form.

And by controllable I mean, if the patient were to experience an exaggerated effect of Fentanyl they can merely remove the unit and stop oral transmucosal absorption. And because of the pharmacokinetic properties of Fentanyl, the analgesia has a relatively short duration which again, is often important for patients with breakthrough pain.

The pharmacokinetics of OTFC were studied in a group of normal volunteers who were administered a dose of 15 micrograms per kilogram in three different delivery forms. On one day they received the medication IV, the next time, oral transmucosal, and a third time they swallowed the dosage form.

And what we found when OTFC is administered over 15 minutes, the peak blood level concentration occurs at around 23 minutes. So five to ten minutes after you finish consuming the unit you will get the peak blood level. The peak blood level in this study was about 2.7 nanograms/ml, and I want you to recognize this as a log access, which compared to a peak blood level after IV administration of 34 nanograms/ml.

And we're often asked, well what happens if

the patient swallows the unit? And in this study, the unit was dissolved in water and the patient swallowed it. And what we find then is that you get a much lower peak on the order of 1 nanogram/ml, and the peak tends to occur much later -- at 90 minutes. Again, this helps illustrate some of the limitations of using oral opioids.

We've also studied the dose proportionality of OTFC in the dosage range that we used in the cancer pain clinical trials -- namely 200 to 1600 micrograms. And what we demonstrated was that OTFC delivered Fentanyl in a dose-dependent manner.

Well, that's some information on pharmacokinetics. What about pharmacodynamics? In a relative potency study that Dr. Portenoy will describe in a little more detail later, we were able to look at the onset of meaningful analgesia. Now, these were patients undergoing lower abdominal surgery who had PCA overnight, and on the next morning their PCA was turned off.

And at their first request for analgesia in a blinded fashion, they received either OTFC or IV Morphine -- high and low-dose OTFC and high and low-dose Morphine. And at the same time they were given a stopwatch and they were asked, when you experience

meaningful pain relief, stop the watch. And by five minutes over 50 percent of patients had experienced meaningful pain relief, and by ten minutes over 80 percent -- both in the OTFC groups and in the IV Morphine group.

Well, how about the duration of analgesia? And in this slide we're plotting the percent of patients who are requiring additional, remedication; in other words, when they would have pressed the PCA button again. What we found in this study is that the two higher doses, the higher dose of OTFC and the higher dose of IV Morphine, provided analgesia with a median duration of about three-and-half-hours -- which was longer than the lower doses of OTFC or IV Morphine which was about two-and-a-half hours.

This study was also designed to look at relative potency, and whether we look at duration of analgesia or the area under the curve of the pain intensity plot, what we found was that the relative potency was about 10:1. The range was from 8-14:1, but a middle number is about 10:1.

In summary then, Oral Transmucosal Fentanyl Citrate represents a non-invasive route of administration that the patient has some control over, that provides very importantly, the rapid onset of

pain relief similar to IV Morphine, on the order of five to ten minutes. Now, that's the onset of pain relief. Many of our patients say that they start to feel pain relief early but the maximal effect occurs really at about 20 to 30 minutes.

The duration is relatively short, on the order of two-and-a-half to three-and-a-half hours in the dosage range of 200 to 800 micrograms, and the relative potency with IV Morphine is about 10:1. Well, what does this mean? This means when we give 800 micrograms of OTFC this is not like giving 800 micrograms of IV Fentanyl; it's more like giving eight milligrams of IV Morphine.

Well, this dosage form has been approved previously for market as Fentanyl Oralet, approved for in-hospital use for anesthetic pre-medication, or for providing conscious sedation or what we commonly refer to now as sedation analgesia prior to painful procedures, in the hospital in monitored anesthesia care settings.

About that time in late '93, we began discussions with the FDA about our cancer pain program which culminated in our initial meeting in April of 1994, when we got together with the FDA, Anesta, Abbott, and two leading pain specialists: Dr. Russell

Portenoy, who at the time was at Memorial Sloan-Kettering; and Dr. Richard Payne who is at M.D. Anderson.

At this point we were able to define the clinical program which provided its own challenges. Prior to this point there had been no clinical trials looking at breakthrough pain, so we weren't, for example, able to make estimates about how much of a response we might see. We weren't able to make power calculations.

Now, an important assumption underlying this program was that Fentanyl is a potent analgesic; that we didn't have to prove that Fentanyl provides pain relief. We were highly focused though, on figuring out dosing guidelines: how were we going to teach clinicians how to use this product in an outpatient environment?

Well, this obviously required a lot of work and a lot collaboration, and we would like to thank the hard work that both the FDA and our consultants put in over the next two years as we designed and redesigned protocols and as we reviewed the data. The controlled, chronic pain trials were completed in July of 1996 and we submitted the NDA last November.

On summary today, we've heard about the

problem of breakthrough pain; how tough it is to manage. We've also heard about the important clinical features of OTFC: the rapid onset of pain relief, in a non-invasive, controllable, delivery system.

The analgesia has again, relatively short duration. And it's these important, clinical features of OTFC which offers the potential that this could be a very effective method or way to manage breakthrough pain.

Well, this is a background. I'd now like to introduce Dr. Russell Portenoy who was a consultant on the HCPR guidelines that were developed and was actually a member of the committee of the ASA who recently developed cancer pain guidelines.

DR. PORTENOY: Good morning. Thank you. I'm pleased to be here and have the opportunity to present the clinical studies that have evaluated the safety and efficacy of the Oral Transmucosal Fentanyl Citrate product. As Steve Shoemaker mentioned, I was actively involved for the past several years in helping the sponsor design these studies. I was also an investigator on several of the studies.

I'm also a clinician who's been heavily focused in the area of cancer pain for more than a decade and have had the opportunity to do some

epidemiologic surveys of break through pain and trying to define the phenomenon in a more clinically relevant way. So I have an intense interest in this formulation, both from a methodological and from a clinical perspective.

It's probably worthwhile then, to just begin with this clinical perspective and then to reiterate some of the points that Dr. Shoemaker made. That cancer pain for example, is highly prevalent and still represents a major health problem. Undertreatment, undermanagement of cancer pain continues to be highly prevalent, and a proportion of patients that is still too high, continue to have unrelieved pain.

It is now widely accepted around the world that conventional, medical practice for the treatment of cancer pain involves the long-term, in-home use of opioid therapy, which typically involves the administration over time of both long-acting and short-acting formulation.

The principle on which this opioid therapy is grounded is the principle of dose individualization through a process of dose titration, which attempts to optimize the balance between analgesia and side effects. This titration has to be accomplished over time, usually repeatedly in the long-term management

of chronic, cancer-related pain. And the goal is always satisfactory pain control with a favorable balance between analgesia and side effects.

Now, breakthrough pain is clearly a highly prevalent phenomenon in and of itself. There are several surveys now that indicate that breakthrough pain occurs in somewhere between 50 and 65 percent of patients who have chronic cancer-related pain. And there's also data now to begin to evaluate the impact of breakthrough pain.

There are two longitudinal prospective surveys that have demonstrated that the presence of breakthrough pain is a predictor of overall bad outcome of opioid therapy for cancer-related pain. And my colleagues and I when I was at Sloan-Kettering, did a survey that demonstrated a highly statistical correlation -- statistically-significant correlation between adverse mood effects and compromise of function and the presence of breakthrough pain in patients with chronic, cancer-related pain.

The prevalence and negative impact of breakthrough pain has been recognized by clinicians for a long period of time, and conventional practices have evolved in an effort to manage it. And conventional medical practice now endorses the use of

supplemental opioid therapy typically used in a short-acting, oral opioid.

And this therapy typically involve the selection of a starting dose empirically, and conventional, medical practice typically endorses the starting dose as a dose proportional to the total daily dose -- typically somewhere between 5 and 15 percent of the total daily dose is used as the starting dose for the breakthrough pain medication.

And then the breakthrough medication is titrated to effect, again with the goal of optimizing the balance between analgesia and side effects.

Now clearly, this clinical, conventional approach to the management of breakthrough pain is empirical based on clinical experience because, before the sponsor began to do studies of OTFC there were no controlled, clinical trials of medication approaches for the treatment of breakthrough pain. And in designing these trials we had to face a number of very difficult challenges.

Breakthrough pain is clearly a very heterogeneous phenomenon; it's an unpredictable phenomenon; and in the vast majority of patients with cancer, it's occurring in an ambulatory environment. It may occur unpredictably out of the observation of

an investigator or a clinician.

In order to do studies where the data would be most generalizable to the clinical setting, those studies had to be done in an outpatient environment; therefore we had to try to study a heterogeneous transient phenomenon which occurred out of the view of the investigator. And this clearly is a challenging thing to do in a controlled and systematic way.

In addition, patients often had severe underlying illness and as Steve Shoemaker mentioned, there were no previous trials to use in an effort to model or do power calculations.

Having said that, we did go ahead and begin to design a clinical program in an effort to determine whether or not OTFC is a safe and effective therapy for breakthrough pain. That program clearly began with single dose and multi-dose pharmacokinetics and dose proportionality studies.

But then the clinical program began, and the clinical program had several important goals. The first goal was to determine whether or not a titration schedule could identify a dose which was effective when compared to placebo.

The second goal was to do a controlled, analgesic potency study in order to identify the

potency of OTFC in relation to the prototype opioid, IV Morphine. And this is really an extension of a line of research that began more than 40 years ago and has culminated in an equi-analgesic dose table that allows clinicians to have some idea about the potency of any opioid in relation to the prototype opioid and that dosing information -- that information is useful when attempting to dose patients.

Finally, two studies were done that evaluated the titratibility of OTFC therapy in outpatients, and attempted to collect some additional information about efficacy, more information about safety, and information that would be helpful in the design of dosing guidelines in clinical practice. And finally, there was additional safety information obtained through long-term surveys of OTFC.

So let me now begin and walk you through the clinical studies in an attempt to focus, first on the methodologies that were developed, and then on the results of these studies.

The first study I'll show you is the placebo-controlled OTFC trial, the aim of which was to demonstrate that OTFC is more effective than placebo for treating breakthrough pain in cancer patients taking stable doses of around-the-clock opioids.

The design was a multicenter, randomized, double-blind, placebo-controlled crossover trial. The patient population were: ambulatory cancer patients living at home who were using an oral opioid with a dose equivalent to 60 - 100 milligrams per day of oral Morphine, or who were using transdermal Fentanyl of a dose of 50 - 500 micrograms per hour to treat their stable, persistent pain -- their baseline pain -- and who were also experiencing one to four episodes of breakthrough pain per day.

The study design was in two phases. The first phase was an open-labeled titration of OTFC and the goal of this was to define a so-called successful dose. A successful dose is a dose at which one OTFC dosage unit would provide adequate analgesia with acceptable side effects.

In other words, it was a clinically-relevant outcome. It was a dosage unit that a patient could take when the target breakthrough pain occurred, and that dosage unit would produce a favorable balance between analgesia and side effects.

The titration approach used here I'll discuss more in a few minutes, but was an approach that began with a low dose, allowed that patient to take multiple doses if the initial dose was

ineffective; but if the patient required multiple doses then the patient could be increased up to the next dosage unit size. So that over a period of days a single, dosage unit size that could treat the breakthrough pain successfully would be identified.

After the successful dose was identified, the patients would enter phase 2 where they were given ten OTFC-appearing doses, seven of which contained the actual drug and three of which contained placebo. They would then choose when to treat a breakthrough pain, but every time they chose to treat a breakthrough pain they would take one of the OTFC-appearing devices and then thereafter, monitor pain intensity, pain relief, go over medication performance and adverse effects.

And 130 patients entered the study, 22 patients withdrew due to adverse events in the titration phase. Dr. Shoemaker will explain these adverse events in more detail in the integrated summary of safety. None of these adverse events was serious.

Other patients withdrew for other reasons leaving 92 patients who completed the titration phase and then entered the double-blind phase; 72 patients completed all ten episodes, crossing over between

placebo and active drug in the double-blind phase of the study.

The patient characteristics of these 92 patients is depicted on this slide and the mean age was 54 with a range of 27 up to 84 years of age. The male/female split was about equal. The mean rate was 70 kilos. And there was a disproportionate number of Caucasian subjects in this study.

There was a diversity of tumor types represented, with the largest numbers belonging to breast cancer, lung cancer, and colorectal cancer, as expected.

The baseline doses taken by these patients -- baseline medications taken by these patients varied. About two-thirds of the patients were taking oral Morphine -- most as controlled release oral Morphine preparation -- about a quarter of the patients were taking transdermal fentanyl.

The mean baseline dose around the clock was 166 Morphine equivalent milligrams per day, with a range of 30 to 600. In addition, all the patients entered the study taking supplemental medications for breakthrough pain, as is consistent with conventional, medical practice. About a third of the patients were using immediate release Morphine; about a third of the

patients were using immediate release oxycodone.

The mean milligrams per dose of rescue medication was 18 Morphine equivalent milligrams, and the range per dose being used to treat the breakthrough pain at the time the patient entered the study varied between five milligrams on the low end and 120 Morphine equivalent milligrams on the high end. This diversity, again, is what one encounters in the clinical setting.

The open label titration phase again, was intended to identify a single dosage unit that could provide adequate relief of breakthrough pain for the patient; with "adequate" being defined as a favorable balance between analgesia and side effects. And depicted on this slide is the distribution of dosage units that yielded that outcome.

And as you can see here, about a quarter of the patients required either 1200 microgram unit or the 1600 microgram unit as the successful dosage unit for treatment of their particular brand of breakthrough pain.

The time action plots for this study, as was mentioned by Dr. McCormick below, did demonstrate separation from placebo. There was a clear placebo effect in both studies and then significant separation

from placebo at all time points where the one evaluated pain relief or pain intensity difference.

The adverse events in this study were as would be expected with any opioid: 22 patients reported dizziness; 17 reported nausea; and 11 patients had somnolence. Three patients withdrew from the study because of an adverse event that was at least possibly related to the OTFC, and as you can see on this slide, these varied: shortness of breath, chest pains, disorientation, unsteady gait, and several others.

Again the adverse events will be described in more detail in the integrated summary of safety that Dr. Shoemaker will do later.

So this study, this placebo controlled study demonstrated in the open labeled phase that a titration approach would seem to be clinically relevant starting at a low dose, allowing multiple units, and then racheting up to a larger dose if patients actually required multiple units; identified an effective dose in the majority of patients -- more than two-thirds of the patients; and then when that effective dose was compared against placebo, it demonstrated that this potent analgesic, Fentanyl, when embedded in this lozenge on a stick, was capable

of providing analgesia with a safety profile that would be consistent with any other opioid drug.

The next study I'd like to present to you was the relevant potency study, the aim of which was to determine the relative potency of OTFC and IV Morphine. The design of this study was again, a multicenter, randomized, double-blind, graded single dose trial in which single doses of OTFC -- 200 micrograms and 800 micrograms -- were compared with single doses of IV Morphine -- 2 milligrams and 10 milligrams.

Now, this study was done in a highly reproducible pain model, namely, post-operative pain due to a lower abdominal incision. Most of the patients in this study underwent gynecological surgery.

The design of this study was that patients would receive routine pain management overnight using patient-controlled analgesia. On the morning following surgery this was discontinued. When the patient reported a level of pain they received a steady drug in blinded format.

And the study drug that could be given would either be 200 microgram OTFC, 800 microgram OTFC, or 2 milligram IV Morphine or 10 milligram IV Morphine,

and a double-dummy approach was used to maintain the blind in this administration.

Following the administration of the drug the patients had a stopwatch and used that stopwatch technique in order to indicate when meaningful pain relief came on, and pain intensity and relief were monitored over time. The need for remedication, the request for remedication on the part of the patient, was used as a proxy variable for duration of effect of these study drugs.

And 133 patients entered this trial. You can see that there was a relatively even match in terms of age across the different groups. The mean weight was about 71 kilos and again, a relatively even split among the study groups.

Most of the patients in this trial were female because of the preponderance of GYN surgery and as you can see, there was a more even mix here between Caucasian and non-Caucasian patients.

If one looks at the time effect curves, the first looking at pain intensity difference, you can see that in the later time points there's a separation by dose with the lower doses of OTFC and Morphine providing less analgesia than the higher doses of OTFC and Morphine.

In terms of duration of effect, this represents the patients who were requesting additional analgesia by time, and you can again, see that there seems to be a separation between those patients who received a lower dose of either OTFC or Morphine, and those who received a higher dose.

And if one created summary variables in order to derive relative potency scores, one can do this either with duration of analgesia or by looking at the area under the curve of the time action relationship using the normalized weighted some of the pain intensity differences through 360 minutes, and you can see that these curves have all the characteristics of a valid, relative potency assay.

They demonstrate dose response between the lower dose and the higher dose, the curves are relatively parallel, and they overlap in the effect range.

So these curves have the characteristics of a valid, relative potency assay, and as was mentioned by Steve Shoemaker before, if one evaluated the different variables in terms of the relative potency, one found the range of scores that vary between 8:1 OTFC to Morphine, and 14:1 OTFC to Morphine, and a middle figure that one I think, would justify

clinically, would be about 10:1 relative potency between OTFC and Morphine in this single dose relative potency assay performed in the post-operative setting.

Now, as Steve showed before, there was some attempt to measure time to the meaningful pain relief, and you see that these curves don't separate by dose; there's no dose effect that can be demonstrated with this particular variable.

And for that reason it's impossible to conclude that there is, in fact, an equivalence in time of onset between OTFC and Morphine. It's possible that there's equivalence; it seems to suggest that; but it may just be a problem with the sensitivity of this particular variable. So we can't say it in any conclusive way. Certainly, OTFC's onset of effect did not lag behind Morphine.

In terms of adverse effects, they would be what you would expect to see in a post-operative setting in patients receiving opioids. Some patients experienced fever, some patients developed nausea, pruritus, and there was no separation between the OTFC and Morphine. And again, this will be discussed in more detail a little bit later.

So the conclusions from this relative potency study is that the OTFC to IV Morphine relative

potency is approximately 10:1, which in sort of practical terms means that 800 micrograms of OTFC is roughly equivalent to 8 milligrams of IV Morphine when given as a single dose.

The onset of pain relief and the duration with OTFC was similar to IV Morphine, although conclusions about onset of relief have to be tentative given the lack of a dose response relationship identified in this study, and OTFC was well-tolerated.

The next two studies that I want to present to you are the titration studies, and these studies were predominantly designed in order to determine whether or not a clinically-relevant titration model could culminate in the use of a single dosage unit that the patients would experience as reliably treating their particular breakthrough pain in a way that yielded a favorable balance between analgesia and side effects.

So the primary aim of these studies was to determine that a titration process can be used to identify a dose of OTFC that safely and effectively treats breakthrough pain in cancer patients receiving around-the-clock opioids.

One study, this first one, was done in patients receiving around-the-clock oral opioids for

chronic pain, and then the next study I'll show you, it was around-the-clock transdermal Fentanyl for chronic pain.

Secondary aims in this study were to compare the OTFC with the usual breakthrough medications, assess dose responses, establish OTFC dosing guidelines if possible, and to define the safety profile in greater detail.

In order to have greater confidence that the efficacy data was valid, there was an effort in these studies to introduce some blinding so that neither the investigator nor the patient who participated in these studies would know exactly what dose they were taking at any point in time.

So the design was a multicenter, randomized, double-blind, dose titration performed in cancer patients using oral opioids that were equivalent to 60 to 1000 milligrams of Morphine per day for persistent pain, and who were experiencing 1 to 4 episodes of breakthrough pain per day.

The design of this study was in three phases. First, patients were assessed in terms of their usual breakthrough pain and the ability of their usual, supplemental, oral opioid medication to manage that breakthrough pain.

And so the patients were assessed during a 2-day observation period, two episodes of breakthrough pain treatment per day were assessed, and what patients were told to do was to complete a diary that indicated pain intensity, pain relief, medication performance, and adverse events for their usual breakthrough pain medication as it worked, as it was used to treat their target breakthrough pain.

Following this phase they entered into a titration phase, the goal of which was to define a successful dose. And again, the term "successful dose" in these studies means a dose whereby a single dosage unit could provide adequate analgesia with acceptable side effects for the patient's particular breakthrough pain. The dose range that was studied was 200 micrograms to 1600 micrograms.

Following titration to a successful dose, the patients then had that successful dose assessed systematically for two more study days. Two episodes of breakthrough pain per day were evaluated on each of these observation days, and just like in the phase 1 period, after each treatment pain intensity, pain relief, medication performance, and side effects were evaluated.

Now, the procedure that was used to titrate

the patients OTFC and thereby find a successful dose incorporated both random assignment and an effort to blind. Specifically, patients were randomized either to a 200 microgram unit or a 400 microgram unit to start and this was done in double-blind fashion -- neither the investigator nor the patient knew what the starting dose would be.

Patients were in close contact with the study nurse and when breakthrough pain occurred they would take one of these units, and if the breakthrough pain was not effectively treated they were allowed then to take a second unit. If that didn't work they were allowed to take a third; if that didn't work they were allowed to take a fourth. They were allowed to take up to four units per episode and to treat up to two episodes per day.

If they needed more than one OTFC to treat an episode, then they were allowed to increase the dosage unit size. The nurse and the investigator would decide whether or not to increase the dosage units, and the pharmacist would be called in order to increase the dose.

When the pharmacist was called to increase the dose, one-third of the time the pharmacist would ignore the order to increase the dose. And this was

done randomly an in double-blind fashion; neither the investigator nor the study nurse nor the patient knew whether the order to increase the dosage unit was ignored or actually proceeded according to plan.

So this continued until patients were titrated and one OTFC was effective on two occasions, and at that point outcome data was collected as I described previously.

In this study 65 patients entered the trial. The mean age was 53; the mean weight was 70 kilos; there was a relatively even split by gender; and the study sample was disproportionately represented by Caucasians.

The tumor types were diverse with the largest number of patients having breast cancer. The baseline medication, the vast majority of patients in this trial were taking oral Morphine -- usually control relief oral Morphine. The mean dose of this around-the-clock opioid medication was 208 milligrams, and the range was 60 to 800 milligrams per day.

In addition to this baseline medication, all patients were taking a short-acting, supplemental medication for breakthrough pain on entry into the study. About half the patients were taking Morphine; about a quarter of the patients were taking Oxycodone.

The mean dose per supplemental medication was 26 Morphine-equivalent milligrams with a range of 5 Morphine-equivalent milligrams up to 100 Morphine-equivalent milligrams to treat an independent episode of breakthrough pain.

And 48 of the patients, or 74 percent, were able to be titrated to a successful dose; that is, a dose were a single dosage usage provided a favorable balance between analgesia and side effects. Eight patients withdrew due to an adverse event, and this will be described in more detail during the summary of safety a little bit later. Five patients were not successful after being titrated up to the 1600 microgram unit size.

The first set of analyses that were done in this study were performed in an effort to determine whether or not we could show a dose response relationship between dose patients who were started on a 200 microgram unit and dose patients who were started on a 400 microgram unit, or in any other way showed dose response.

And the reason to do this is that the finding of dose response will make us more confident that we had a valid analgesic assay and could then draw some conclusion about the efficacy data that was

collected in this trial.

You could see that the dose that was ultimately reached as the successful dose for those patients who were started at 200 micrograms and those patients who were started at 400 micrograms, was similar. There was no statistically significant different between the final dose among the patients started at the low dose or no starting dose.

However, if you look at the number of titrations that were needed to reach that successful dose, then those started on 400 micrograms. So the finding that those started on the lower dose required an additional titration to reach the successful dose than those started on the higher dose, is supportive of the idea of the dose effect -- a dose response effect.

Another way of looking at this is to look at what happened after a dose was ignored -- after the order to increase the dose was ignored. This happened 15 times in the study, and in 12 of these patients an increase in dose was subsequently needed in order to identify a successful dose.

This again suggests that there was in fact, a dose response relationship so that if the patient and the investigator decided the patient needed a dose

increase to get to a successful dose, he or she actually did require that and subsequent dose titration was necessary to bring them to that level.

And finally, if one looked at the effect data -- pain intensity, pain intensity difference, pain relief, and medication performance -- and compared the effects obtained at the first dose with the effects obtained after dose titration at the last dose within each patient and look at that analysis, not surprisingly, one finds that the effects produced by the higher, last dose, are statistically significantly more than the effects produced by the lower, initial dose -- again, supporting the notion that this study was able to show dose response and therefore we could say something about the efficacy data in a more valid way.

Well, the first and I think, most important analysis from this study evaluated the relationship between the successful dose required to treat breakthrough pain and the baseline dose of opioid medication that the patient entered the study with.

Now, as I mentioned to you before, conventional medical practice usually suggests that the dose of breakthrough pain medication ought to be a proportion of the baseline dose. This is what most

cancer pain guidelines suggest and this is what most people do in clinical practice.

And indeed, if you look at the relationship between the dose of the around-the-clock medication and the dose of the breakthrough pain medication at the time the patients entered into the trial, there was in fact, a statistically-significant direct relationship wherein 63 percent of the variance of the breakthrough pain medication dose could be explained by the baseline dose.

So conventional medical practice was illustrated by this relationship from these patients who entered into this trial. But after successful titration, if one evaluates the dose of OTFC the patients ended up on as a function of the baseline dose rather than this direct relationship, what we found in this study was that there was no relationship. The relationship was not statistically-significant and only the amount of variance explained was .5 percent.

And this reflects I think, the possibility that this study has demonstrated for the first time that conventional thinking about dosing of breakthrough pain medications may not be accurate; it needs more study. This is a new science that was

demonstrated by this trial. I find this very fascinating and important because I've been dosing breakthrough pain medication as a proportion of the baseline dose for a long time and I need to rethink that. It's possible that that's not an accurate, reasonable thing to do.

And the other implication I think, which is very important, is that it suggests that one is not going to be able to pick a dose of OTFC as a clinician based on the baseline dose; that patients are going to have to start at a low dose and then be titrated to an effective dose, and therefore, a conservative approach to dosing which would include a low, initial dose and dose titration, is the appropriate method for treating breakthrough pain using OTFC.

If one looks at the efficacy data -- again, this comparison again, is between the OTFC phase and the patient's usual medication; it's really an open label comparison -- it suggests that the patient found that the OTFC did product analgesia with an onset of effect that seemed to be faster than the usual breakthrough pain medication.

Another way of evaluating that is to look at the amount of pain relief reported per unit time. For example, the OTFC yielded 56 percent of the total

amount of pain relief in the first 15 minutes, as compared to the usual breakthrough pain medication which provided only 34 percent of its total pain relief in the first 15 minutes -- suggesting that the OTFC has a faster onset.

The adverse events in this study, as would be expected, were those that one encounters with an opioid drug. A quarter of the patients were sleepy, 14 percent reported dizziness, 8 percent reported nausea, four patients withdrew with adverse events that were at least possibly related to the OTFC, and these included somnolence, dizziness, hallucinations, body numbness, and so forth. And more detail about this will be coming in a minute.

So the conclusion for this dose titration study was that dose titration can indeed, identify an OTFC dosage unit that safely and effectively treats breakthrough pain in patients receiving around-the-clock, oral, opioid therapy.

The optimal dose of OTFC is determined by titration and is not predicted by the around-the-clock dose. The onset of pain relief appears to be faster with OTFC as compared with the typical, oral, supplemental opioids. And the most common side effects -- somnolence, nausea, and dizziness -- are

typical of opioids and did not limit OTFC use.

Now the second study that was done was another titration study where the methodology was identical to the previous study but it was done in patients who were receiving transdermal Fentanyl. Again, the aim was to demonstrate that a titration process can be used to safely identify a dose of OTFC that effectively treats breakthrough pain in cancer patients receiving around-the-clock opioid therapy.

And the secondary aims were to compare OTFC with the usual breakthrough pain medication, assess the dose response, establish OTFC dosing guidelines if possible, and define the safety profile even further.

The design again, was a multicenter, randomized, double-blind, dose titration study in cancer patients using transdermal Fentanyl in a dose range of 50 to 300 micrograms per hour for persistent pain, and who were also reporting somewhere between 1 and 4 breakthrough pain episodes per day.

The methodology was exactly the same as before. The supplemental medication that the patient entered the trial with was first assessed in a systematic way for two days, two episodes of breakthrough pain treatment were assessed on each of those days, and each treatment was assessed in terms

of intensity, pain relief, medication performance, and adverse effects.

Then the patient entered a titration phase with the guidelines I indicated before, and then after a successful dose was identified, a single dosage unit that could successfully treat the breakthrough pain, the patient had a 2-day observation period, two breakthrough pain treatments per day were evaluated in terms of pain intensity, pain relief, medication performance, and adverse events.

In this study the mean age was 59; the mean weight was 67 kilos; again, there was a relatively even split by gender; and Caucasians were disproportionately represented.

Tumor types varied and the most prevalent tumor type in this study was lung cancer, which occurred in about a quarter of the patients.

All the patients in this study were taking transdermal Fentanyl. The around-the-clock dose of this transdermal Fentanyl had a mean of 103 micrograms per day, and the range was 50 to 300, which was stipulated by the protocol as the range to be studies.

In addition, all the patients in this study were receiving a short-acting, oral, opioid drug for breakthrough pain at the time they entered the study

-- About a quarter of the patients receiving Oxycodone, about a quarter of the patients receiving Morphine -- and the mean milligrams of Morphine-equivalent milligrams taken to treat an episode of breakthrough pain was 21, and the range was from 5 to 100 milligrams per breakthrough pain episode.

Of the 62 patients who entered the study, about three-quarters could identify a successful dose of OTFC; 6 patients, or 10 per cent withdrew due to an adverse event -- three of which were related to the OTFC and will be discussed shortly. Four of these patients were not successful despite titration to the highest dosage unit available, specifically the 1600 microgram unit.

Now, in this study the effort to identify a dose response so that we could have a greater degree of comfort with the validity of the efficacy data, demonstrated equivocal results. And the reason that the results were equivocal is because methodologically we inserted one change in the protocol for safety reasons and that ended up compromising our ability to demonstrate a dose response.

Specifically, it was decided that patients who were taking either 50 or 75 micrograms per hour of the transdermal Fentanyl should not be randomized to

get either 200 or 400. And the reason for that was because we had worked under the assumption that there a proportional need between the breakthrough pain medication and the baseline medication, and that 400 micrograms as the breakthrough pain medication would be excessive for patients who were already receiving only 50 or 75 micrograms.

For that reason, patients who were receiving either 50 or 75 micrograms of transdermal Fentanyl were simply assigned in open label fashion, to get the 200 microgram unit. Unfortunately, when the tallies were all finalized here, you can see that more than half the patients were simply assigned to get the 200 microgram unit, and that randomization was only performed in 29 patients -- 18 of whom were randomly assigned to the 200 microgram unit and 11 of whom were assigned to the 400 microgram unit.

And so when one looks at the analyses that were performed to demonstrate a dose response relationship, the results are equivocal and do not provide a high degree of confidence that we can say that the efficacy data is valid.

For example, the final dose that was titrated to by patients randomized to 200 and 400 microgram, couldn't be said to be statistically non-

significant. The number of titrations for patients randomized to 200 were not more than the number of titrations for patients randomized to 400.

Fifty percent of the time that a dose titration order was ignored, the patient then got successful relief on the same dose. In contradistinction to the previous study where the ignore order typically required the patient to then be subsequently titrated to a higher dose, in this study 50 percent of the time the same dose was effective.

On the other hand, if one looks within patients and evaluates the effect data of pain intensity, pain intensity difference, pain relief and medication performance in terms of the effects produced by the low dose -- the first dose -- and the next the successful high dose, then there is a clear and highly statistically-significant difference in the effects produced by low dose and high dose.

So whereas these type of data suggest that there was in fact, a dose response, the other analyses we performed weren't confirmatory, and for that reason the effect data in this study has to be viewed in a more tentative way.

Another unusual characteristic -- potentially unusual characteristic in this study --

was that there was actually not a very good relationship between the baseline dose and the around-the-clock dose of those patients who entered into this study, in terms of their usual, supplemental medication.

The amount of the variance in the dose of the breakthrough pain medication explained by the baseline medication, was only 22 percent -- in contrast to the previous study where the relationship was much stronger.

Notwithstanding this, if one looks at the OTFC and the relationship between the breakthrough dose and the baseline dose, once again very little of the variance is explained suggesting again, that a conservative and appropriate approach to dosing OTFC is approach that incorporates a low, initial dose in dose titration to the successful dose.

Again, the efficacy data could be evaluated in an open label comparison of the previous dose compared to the OTFC dose, and the OTFC appears to work as well as the usual medication -- actually better -- and that more of the effect of the OTFC is seen earlier, consistent with a faster onset of effect.

And the side effects again, are those that

one would expect from an opioid drug, including sleepiness, nausea, dizziness, and vomiting. And these adverse events will be explained in more detail shortly.

So the conclusions for this study was that dose titration can identify an OTFC dosage unit that safely and effectively treats breakthrough pain in cancer patients receiving transdermal Fentanyl. The optimal dose of OTFC should be determined by titration and cannot be said to be predicted by the around-the-clock dose.

The onset of pain relief does appear to be faster with OTFC compared to the usual breakthrough pain medication used by the patient, but this sort of analysis has to be viewed as tentative in this particular study -- much more strongly supported in the previous study. The most common side effects -- somnolence, nausea, dizziness, and vomiting, are typical of opioids and did not limit OTFC use.

And finally, I would like to just present to you the long-term open-label survey that was done, the aim of which was to evaluate the long-term safety and efficacy of OTFC in cancer patients with breakthrough pain. This again, was a multicenter study and was designed as an open-label survey.

Any adult outpatient with cancer who successfully completed one of the titration trials of OTFC, and who continued to experience breakthrough pain, were allowed to enter this trial. It was their option to enter as long as they successfully completed a titration study and still experienced breakthrough pain.

If they decided to enter the study their around-the-clock medication was simply continued and they started OTFC at the successful dose determined from their previous titration study. They were allowed to treat up to four episodes per day and if necessary, OTFC was titrated as clinically indicated.

The number of breakthrough pain episodes per day, the medications used to treat breakthrough pain, the global satisfaction with the OTFC, and side effects were monitored as outcome. In this study there were 155 patients. The gender split was about equal; the mean weight was 69 kilos.

You can see here that the age mix was quite broad. The age range of the patients surveyed was from 26 to 91 years, and 22 percent of the patients were over the age of 65; 93 percent of the patients were Caucasian.

The patient exposure to OTFC in this survey

is as follows: 92 percent of the patients who were eligible to participate in the extension trial, opted to do so; the number of treatment days ranged from 1 to 423; the mean number of treatment days was 92.

There was an average of 2.5 episodes of breakthrough pain per day treated with the OTFC. This culminated in usage of 41,766 OTFC units consumed and 38,595 episodes of breakthrough pain treated during the extension trial.

The results of the trial were as follows. Patients experienced on average, about three episodes of breakthrough pain per day and as I said before, 2.5 of these episodes were treated with the OTFC at the patient's discretion. The could choose to treat the breakthrough pain with the OTFC or not at their discretion.

And 92 of the episodes were successfully treated with OTFC, with success being defined as an adequate result -- in other words, a favorable balance between analgesia and side effects -- being obtained with a single dosage unit of the OTFC.

The patients rated mean medication performance on a 4-point scale at 3.1, and over the course of time during this study period, 66 percent of the patients remained on the same or lower dose.

There was no tendency for patients to require higher and higher doses over time. Or limited tendency.

If you look at the distribution of doses taken by patients, you'll notice that this all adds up to more than 100 because some patients would take a lower dose and then be titrated up to a higher dose. But you can see that about 50 percent of the patients ended up taking 1200 or 1600 microgram unit doses.

And if you look at the episodes treated by unit dose you'll see that about 35 percent of the episodes of breakthrough pain were ultimately treated with either the 1200 or the 1600 microgram dose.

The safety data will be described again, in more detail. If you just look at the items below this dotted line, these are adverse events that were possibly related, probably related, or almost certainly related to the OTFC. There were no serious, adverse events associated with the OTFC.

There were a few withdrawals associated with OTFC which will be described in a few minutes, but by far the most common side effects related to those that you typically see with opioid drugs: somnolence, constipation, nausea, dizziness and vomiting. The adverse events that led to patient withdrawal included itching, rash, nausea, vomiting, dizziness, and mouth

sores.

So the conclusions from this long-term open survey was that OTFC was used safely and effectively to treat breakthrough cancer pain; over 41,500 units were used; over 38,500 breakthrough pain episodes were treated; and patients used the OTFC for up to 423 days of therapy.

The satisfaction ratings were good, there is no trend toward decreased effectiveness over time, and the toxicity profile was favorable with few withdrawals related to OTFC.

Thank you very much.

DR. SHOEMAKER: In just a moment we'll conclude the clinical discussion with an overall summary of the safety data.

As Dr. McCormick pointed out early, in addition to the 257 cancer patients reported in this NDA, we also looked at data from 212 post-operative pain patients and 48 volunteers that participated in pharmacokinetic studies.

I think it's very important to understand that these post-operative pain patients were not studied in a setting looking at OTFC to treat post-op pain. These studies were done to define the analgesic properties for OTFC.

For example, some of these were Morphine-sparing studies were patients were actually receiving IV Morphine at the same time they were receiving OTFC, and they were receiving OTFC on a time-contingent basis; for example, every six hours or every eight hours, as opposed to a PRN basis which is how you would commonly treat post-operative pain.

Again, if we look at the overall patients, over 22 percent were over the age of 65, meaning the elderly were well-represented. There was only a slight predominance of women in these studies and again, the vast majority of these patients were Caucasian.

There were multiple cancers represented in these patients, but if we look at the top three, breast and lung were clearly the most common with colorectal being the third, and these solid tumors which commonly metastasize to bone then, represented about 50 percent of these patients.

If we look at the dosage strengths that were used in these trials, in the controlled trials -- now, these are the titration trials -- we obviously have a lot of patients using the lower dosage strengths because this is where we started the titration. And again, these numbers add up to greater than 100

percent because you could have been titrated up all the way through, up to 1600 micrograms.

Now, when we look at the long-term trial, the long-term safety trial -- these are patients that had already been titrated to an effective dose -- and we see a more equal distribution again, with good representation at the highest two dosage levels.

Now as was pointed out, in the titration phase of these studies as you were trying to find your successful dose, it was possible to use more than one unit to treat an episode of breakthrough pain. So now we're looking at the total dose per episode that was used in these titration trials and what we notice is, there were a fair number of patients who used over 1600 micrograms.

And as was also pointed out earlier, the largest number of micrograms that was used was 7200 micrograms which was used over about four hours with no adverse events reported on that day.

If we look at the number of units administered -- actually used in these trials -- again, in the controlled titration trials there tends to be more predominance at the lower doses as patients begin the titration process, but if we look at the number of units used -- and I'll point out the fact

that there's an order of magnitude larger units here than here -- in the long-term trial again, patients are using more of the higher dosage strengths.

Now, the adverse events that we saw in these patients are those typical of opioids. And it must be remembered that patients on this trial were often on two to three different opioids. They could be taking a different opioid -- for example, sustained relief Morphine -- for their persistent pain.

And if we look at events that the investigators felt were related to OTFC, the expected opioid events that we saw greater than ten percent were nausea, dizziness, and somnolence.

This is combined data now, on the titration trials, the control trials, and it must be remembered that these patients had cancer. They were often very ill; you'd expect them to have adverse events. These patients often got hospitalized for example, for problems with their underlying cancer.

When we look at withdrawals due to adverse events, over half of these were unrelated to the use of OTFC. If we look at serious adverse events -- including deaths -- there were only four episodes that could be considered possibly related to OTFC. I'd like to spend a little bit of time now on that one

patient that I showed up there where it said the death could be possibly related.

This gentleman was a 62-year-old, white male with advanced, chronic, obstructive pulmonary disease. In 9/95 he was diagnosed with adenocarcinoma of the lung and at the time of pleurectomy was found to have metastatic adenocarcinoma involving the left diaphragmatic pleura. He underwent a parietal pleurectomy with decortication.

His course was complicated by the fact that he had an episode in November of 1995 of deveinous thrombosis and pulmonary embolus at a time that he was on Coumadin therapy. In February of 1996 he developed progressive shortness of breath and a repeat evaluation was done.

On CT scan he had dense consolidation of his entire left lung, there was some volume loss suggesting that there might be a central lesion. However, on bronchoscopy there was no central endobronchial lesion found. So this gentleman was essentially working on only one lung, his right lung, which had been compromised by chronic, obstructive pulmonary disease.

His oxygen saturation fell from 91 to 87 percent with minimal exertion, and at this time he was

started on home oxygen therapy at 2 liters per minute for his shortness of breath. His medications at the time he entered the trial: he was using MS Contin for his around-the-clock pain; he was using Percocet for his breakthrough pain; he was also taking Prednisone for his rheumatoid arthritis; he was also on Digoxin; he had been switched to Heparin because he had filed the Coumadin therapy; and was also on these other medications including Lasix.

The slides are a little out of order; I apologize for that. Now, after that evaluation for progressive dyspnea and being started on home oxygen therapy, he entered a titration trial on February 29th starting at a dose of 200 micrograms. By 3/2/96 his dose had been increased to 600 micrograms, and between 6 and 7 o'clock in the morning he took 3 units.

Later on in the day he took two 800 microgram units with slight relief of breakthrough pain, and later on in the day took a 1200 microgram unit and reported lots of relief within 15 minutes. So this is an example of a patient who was being titrated at home, increasing his dose.

Now, he had developed over this day, increasing shortness of breath throughout the day without a clear temporal relationship to taking his

dose of OTFC. On the next day early in the morning, he took a 1200 microgram unit with lots of relief at 30 minutes; he took another one at 0900, and described during this day that a shortness of breath that had started earlier, was again progressing, again without a temporal relationship to his OTFC.

At 10:30 in the morning his dyspnea had progressed to the point that his wife felt that she should take him to the emergency room, and the patient died while traveling to the hospital. The investigator felt that this patient's death was due to respiratory arrest secondary to metastatic lung cancer, and felt just because he had recently been started on OTFC, that it could possibly have been related to the study drug.

Now, if we look at the withdrawals due to AEs and the serious adverse events in the long-term trial it's important to remember, now these are patients that have already been titrated; they've already found a successful dose. And as Dr. Portenoy pointed out, there was just a handful of withdrawals due to adverse events that would be considered related to OTFC.

But in these patients who had been successfully titrated there were no serious AEs that

can be considered, possibly or even probably related to OTFC. Also notice that 31 patients died during the long-term trial. Again, these are patients with cancer; their disease progressed.

But the point here is also that these patients were able to use OTFC not only during the active phase of therapy, but were often able to use OTFC as their disease progressed, right up until the time of death.

Now I'd like to switch and talk about the opioid non-tolerant patients that were included in this NDA. Now, it's very important to understand that the risk profile is different in these non-tolerant patients. These patients have not had an opportunity to develop tolerance to some of the opioid side effects.

Now, the most clinically-important side effect obviously, is respiratory depression. Whereas it's possible for a chronic pain patient to be on grams and grams of morphine a day and not suffer any respiratory effects, in opioid non-tolerant patients we expect to see dose-dependent respiratory effects. This is a common property of all opioids.

I'd also like to point out once again that in the post-operative patients, 45 percent were on

concurrent IV Morphine at the same time they were taking those OTFCs. So two potent mu-acting opioids was not always easy to distinguish, which might be causing an effect.

Now in the volunteers we didn't have this complication of concurrent medications, but these patients also were not in pain, which may also affect their susceptibility to opioid-induced respiratory effects.

Well, what did we see? These are the adverse events that were seen in the post-op patients -- and again, these are patients who were receiving OTFC, these are patients who received placebo in the Morphine sparing studies, and these patients receiving IV Morphine then, were in the relative potency assay.

And what we notice is that incidents of nausea of 57 percent, and of high clinically-diagnosed hypoventilation of 18 percent that's higher in the placebo group in the OTFC, is probably again, reflective of the fact that these patients were on another potent opioid.

Let's focus a little bit on respiratory effects because again, this is the clinically most important side effect that we're interested in. Twelve percent of the patients were diagnosed with

clinical hypoventilation, either because they desaturated or the respiratory rate was low.

And if we break down these patients and look at where this hypoventilation occurred, most of it occurred in the 800 microgram dose of strength -- which perhaps is not surprising seeing the dose response that we'd expect. And these were the two patients -- the only two patients of this study that received Naloxone.

And again, as I stated earlier, the protocol called for giving these medications every six hours or every four hours for example, and not on a PRN basis.

If we turn to volunteers now and focus on respiratory effect we saw on volunteers, again we saw an incidence of clinically-diagnosed, hypoventilation of 40 percent -- diagnosed by whether their oxygen saturation fell, whether the respiratory rate fell, or whether they required prompts to breathe, to support their oxygen saturation.

And if we look at successfully increasing doses we see that the incidence tends to increase. The same is true if we look at the number of volunteers that required supplemental oxygen. Now, none of these patients required Naloxone, and usually these desaturations -- especially at the lower doses

-- could be managed by prompting the patients to breathe.

In summary then, we looked at 257 chronic pain patients that were opioid tolerant. We used over 45,000 units in these patients for up to 423 days. The elderly were well represented in this trial, and OTFC was looked at in all stages of disease progression -- when patients were relatively active and as they developed debilitating disease and eventually died.

The most common treatment-related AEs that we saw are those expected of opioids, namely nausea, somnolence, and dizziness. And in our opioid non-tolerant patients what we saw was expected dose-dependent, respiratory depression.

Now, because we have not determined a safe and effective dose for using OTFC in the post-operative pain environment, we are recommending that there be warnings in the black box that the use of OTFC is contra-indicated for the treatment of acute pain or post-operative pain.

Well, this then, concludes our discussion of our clinical program, a very comprehensive program that included pharmacokinetic studies in volunteers -- for example, to demonstrate dose proportionality. We

also had studies in a very defined population -- a controlled environment of lower abdominal surgery post-operative pain, to look for dose response effects and to assess the relative potency.

And in our cancer pain trials we felt that it was very important to study these patients at home in the outpatient environment. Now, we all know there's some limitations to doing trials there. These patients are ill; there are limitations to how much data you could ask them to collect. However, these patients were able to rate pain intensity differences, pain relief changes.

We were able to demonstrate that *Actiq*™ provides significantly better pain relief than placebo after using a titration protocol very similar to what we will be recommending. In other words, start low. Start at 200 micrograms. You can use multiple units for an episode but if you require more than one unit you should go up by one dose of strength.

And in the other studies that we did we also had a comparison to the patient's typical breakthrough medications. These were open-label comparisons, but the differences that we see were highly significant. It appeared that *Actiq*™ was providing more pain relief sooner.

At this point I would now like to introduce Dr. Clair Callan of Abbot Laboratories who will discuss our Risk Management Program.

DR. CALLAN: Good morning. Professor Downs and members of the Advisory Panel, it is a great pleasure for me to be here today to discuss with you the Risk Management Program that is a very key component of this product.

As you know, most of you, I am the Vice President of Medical and Regulatory Affairs for the Hospital Products Division of Abbott Laboratories, and Abbott is very pleased to be collaborating with Anesta in bringing this very important product to the marketplace.

We need to remember that all opioid therapy benefits come with potential risks. And we have focused particularly with this product on the issues concerning child-safety, opioid non-tolerant patients, and diversion and abuse potential.

Child safety has been a major factor in our consideration of this product from the start because we're aware that this is, as we have heard very eloquent testimony from some of our patients, this could be considered a precious product for the cancer patient.

It is providing them the ability to re-enter into their regular life, to gain back some control over their life, and for that reason we are determined to do whatever we can to make sure that this product that is so valuable, continues to be available to cancer patients who need it by maximizing the safety attention to prevent the abuse by children or other people.

We also realize that it is important to minimize the potential for product misuse, and our goal with the program, the innovative Risk Management Program that we have developed in conjunction with Anesta, will provide appropriate child safety protections, emphasize the approved indication for the marketing of this product, and minimize diversion and abuse.

And one of the reasons that I am here presenting this Risk Management Program is to emphasize to the committee and to the FDA, the importance that Abbott Laboratories places on this Risk Management Program and the commitment that we are making to make sure that it is enforced.

The potential misuse, or the actual misuse of any opioid by a child is indeed a very serious situation. And as I've said already, we are taking

several steps to focus on preventing the ability of children to get at this product. Abbot and Anesta hope to become leaders in the education of people about the dangers of drug misuse or accessibility, and particularly in the home.

And we can use this product as an example to establish standards for safe, education, or attention to educational components that will draw attention to both patients, caregivers, and anybody else who's involved with using opioids or other strong medication that should not be accessible to children.

We have taken particular steps to make sure that this particular product is available only in child-resistant pouches that cannot be opened by children. This has allowed us to emphasize the need to keep medication out of the reach of children and in fact, we have put together some words that demonstrate the product, which are up here behind you. Maybe at the break you could have a look at them.

But represented there is each individual pouch which represents one dosage unit, and on that it clearly states, keep out of reach of children. Those pouches go into a box and the box also states that it should be kept out of reach of children.

We also have developed educational materials

that will be directed at both clinicians and patients, including their caregivers, that emphasize the importance of keeping this medication out of the reach of children.

The fact that we have developed multiple dosage strengths is another safety factor. Our goal is to make sure that an individual unit will be sufficient to control a patient's pain, so that there will not be the opportunity to partially consume a unit, put it aside and use it later.

The patients are clearly instructed that once they have completed using this unit for one episode of pain, that they are to dispose of it, and they're given instructions on how to do that. And there are clear and repetitive disposal instructions provided in the patient care information that we give them, plus the aids that are being handed out in the counseling they get from their physician when the product is being prescribed.

We have these three labels pretty frequently through all the materials that have been developed in association with this product, including the package insert, the patient package information insert, all of the educational materials, the labeling as I indicated to you.

And these are -- well the first one is a pretty standard one that says, "Keep this and all medications out of the reach of children". We also have, particularly in the patient information insert, "Be sure to keep *Actiq*™ away from children. *Actiq*™ contains a strong medicine in an amount that could be life threatening to a child".

And also we frequently warn patients not to leave unused or partially used *Actiq*™ in places where children can get to it. And again, the emphasis is on teaching patients to dispose of the unit as soon as they have completed using it.

The disposal information is as you see here. It is pretty simple to get rid of *Actiq*™ by just holding it under warm water and it very quickly dissolves and drains down the sink. And then they're instructed to throw away the handle.

They're also instructed to dispose of any *Actiq*™ as soon as they no longer need it, and again they're reminded not to leave unused or partially used units in places where children or pets could get to it.

Prevention -- the patient and caregiver education focuses very heavily on this too -- the importance of not allowing children to get near the

product. There is a comprehensive instruction program that has been developed for the physicians to use when they're prescribing the product for the patients, and their office staff are also going to be instructed to make sure that they emphasize this aspect.

The patient education materials I've already mentioned. The pharmacy counseling -- when the patient goes to get their prescription filled from the pharmacist, the pharmacist has been asked to do some additional counseling to make sure that the patient understands the seriousness of this product and recognizes the responsibility of keeping it under control.

And we did hear from one of the patients this morning that he is very conscious of the need to keep opioids out of the reach of his grandchildren when they come to visit them.

There's also a warning, again as I've mentioned, on the dispense pharmacy package, in the patient instructions, and on the pouch which is the point of use for the patients.

And this may seem repetitive, but we are repeating this so many times because we want to get the message across that this is a product that is a strong medicine that could cause problems for children

if they inadvertently get into it, and that it is everybody's responsibility to make sure that that doesn't happen.

If we compare what we have done with *Actiq*™ in an effort to protect it from children getting at it to the currently schedule II oral compounds that are out there on the market, the first point I would like to point out to you is that *Actiq*™ is always dispensed in child-resistant packages, whereas the other oral products, this is an optional feature. Not every pill comes in a child-resistant product; not every oral liquid comes in a child-resistant package.

Each unit of use of *Actiq*™ is child resistant, whereas with the oral products that's not true. We believe that if a child consumes *Actiq*™ it's easier to detect that then an oral product because of the fact that the unit is on a stick and the stick is visible.

We also have provided, again, patient instructions detailed to alert the patients of their responsibility to keep this out of the reach of children; and with child-safe warnings on each unit and the black box warning that we have -- and I will describe in more detail -- is present for our product but not for the current schedule II oral products.

We've also strengthened the language in the package inserts. Instead of a gentle word such as "should" or "should not" we're putting in a much stronger word which says "must" or "must not", associated with prescriptions. And as you heard earlier, if this unit is chewed there is not an increased risk of toxicity with *Actiq*™ whereas there is for sustained orals.

The second -- so that summarizes all of the steps that we have taken to make sure that children are protected from inadvertent use of this product, and we believe that we have a very strong program, unlike any other compound that is currently available that is going to heighten the awareness of the clinician as well as the patient and the caregiver to the dangers of this drug if it's not used correctly.

Moving on the possible misuse in opioid, non-tolerant patients, the first risk management part of this is the package labeling -- the product labeling -- which clearly indicates that this is a product that's for use in opioid-tolerant patients only. It is specifically contraindicated for post-operative pain or for acute pain, including post-operative pain, and this is stated in the black box warning.

And again, the use of the "musts" in lieu of "shoulds", and the black box warning I will show you in detail what we have proposed there.

That *Actiq*™ is indicated for the management of chronic pain, particularly breakthrough pain, in patients already receiving and who are tolerant to opioid therapy.

Because serious or life-threatening hypoventilation could occur, *Actiq*™ is contraindicated in the management of acute or post-operative pain. This product must not be used in opioid non-tolerant patients.

Appropriate patient selection and access is our key objective as we move into our promotional program. The promotional efforts will be focused on physicians who treat cancer pain, but we will also educate physicians in the general physician population or others who might be in the position to prescribe opioids, to discourage inappropriate use.

The target clinicians that we are going to focus our promotional efforts on include those that are treating cancer pain right now, which are the Hem/Oncs and cancer pain specialists, and we will also be supporting -- targeting our educational efforts on their nursing support staff.

At launch we will have a very comprehensive educational program which will include direct mail information that we will send to them detailing what the product is and what the safety issues are. There will be an electronic instructional program which will include continuous education credits, which would be one way of monitoring who is taking the program.

We will make a CD ROM available which will have all of this information to be sent to every physician that we anticipate will be prescribing the product. We will have information on the Web site which will be available to these physicians.

We will have professional journal supplements which will have articles detailing what the product is and again, emphasizing the need to be careful with it. And symposia which have already been conducted for the last year will continue at local, state, regional, and national meetings.

And there will be complementary programs for all of the pharmacists, the nurses, and patients, including their caregivers.

For those who are also identified as opioid prescribers but are not necessarily dealing with cancer pain, we will be sending educational letters on the appropriate use of this drug and will emphasize

the warning information and will make the electronic programs that we develop also available to them so they can continue to be educated.

The pharmacist is going to play a key role in preventing misuse or inappropriate prescription for this product. We have developed specific educational programs for them including special symposia for retail chain pharmacists who don't usually attend the professional meetings where a lot of this information is presented.

The fact that this will be a schedule II drug will mean that it will get particular attention or any prescription will get particular attention from the pharmacist.

Computer system reminders and controls are another option we have. We expect that when the pharmacist enters the prescription for *Actiq*™ into the computer, this should also come up that patient's record should indicate that that patient is already on opioid therapy, and if there is no such record the pharmacist will be expected to contact the physician to make sure that the prescription is in fact, appropriate.

And we are working with a system where there will be a pharmacy software program that, when they

enter in the name *Actiq*™, a warning message will automatically come up on the screen saying, check for other opioid prescriptions.

The warnings on the shelf carton of the pharmacy will also be a reminder that this is a schedule II drug and that it needs to be kept out of the reach of children. And the pharmacist will play an active role in counseling the patient, making sure that the patient understands what the prescription is and how they should be handling the drug and how they should be disposing all this when they complete use of it.

The patient is the final step in preventing misuse. And again as I said several times, the educational materials will detail how this should be used by the patient and disposed of. Patient package insert actually has a statement in there that says -- remind the patient that this is a strong medicine that should only be taken if they're already on opioids or other strong medication. And if they are not on such strong medication they should contact their physician before they actually take the product.

And again, the warnings on the pouch and the shelf carton will remind them, and the counseling that they're going to get at the time of the prescription,

or at the time that they pick up their prescription from the pharmacist.

Moving on to preventing diversion or abuse -- and again I have to remind everybody that all opioids have abuse potential and this is not a product that is any different from that. But the fact that it is a schedule II drug will provide additional accountability and control, and the abuse liability assessment involves both pharmacology and availability.

And just to remind you what a schedule II status for a drug entails: it's a very restrictive schedule; no refills are allowed when these products are prescribed; there's limited, if any, telephone or fax prescriptions involved.

The pharmacist is required to ensure that there is a legitimate medical purpose before he dispenses a schedule II prescription that he receives. And there are also onerous record keeping requirements and inventory requirements to make sure that there is no unaccounted-for drug.

The speed of onset and duration of action affect abuse liability of any drug that has this potential, and *Actiq*™ has a speed of onset that does in fact, favor abuse potential compared to oral

opioids, but however, the short duration does mitigate the use to maintain addiction.

And just to summarize for you the difference of the profile between *Actiq*™ versus other schedule II drugs, it's in the middle between the speed of onset -- IV being the most rapid and oral being the slowest -- and the duration of action -- IV being shorter than oral.

Other options that help to diminish abuse potential is the accessibility , and again, because it is a schedule II there are restrictions to its accessibility.

The other point to notice is that patients who are receiving *Actiq*™ or being prescribed *Actiq*™, are already involved with schedule II drugs -- and that's another point to make about the fact that it's coming into these patient's homes. These are patients that are already involved with opioid drugs and have learned how to deal with them in their home.

The cost of *Actiq*™ is going to be more expensive than Morphine equivalent and this can be a deterrent to somebody who wants to abuse it. The packaging itself -- as you will see when you have an opportunity to look at it -- it's relatively bulky and it's very obvious; it's not easy to hide. And the

individual units are going to be audited and counted and if any of them disappear it will be noticed.

And the fact that it takes 15 minutes of consumption for maximum effect and the obvious handle, are other areas that can protect against abuse.

Now this slide is a busy slide and your eye chart for the morning, and it summarizes what we have done in the risk management program to prevent against possible risk. The three columns here are the three risk areas that we have focused on, mainly: the child accessibility -- protecting against it; the use in the opioid naive patient; and diversion and abuse.

And down on this side you will see the plan elements that I have discussed, that shows where in this risk events these element s are focused. And you can see that for all of them, the plan elements really address the possible risk exposure and how to avoid it, the package insert has the black box, the patient package insert, the carton warnings, the product warnings.

The child-resistant pouch and the handle design, while they address the child accessibility more than the opioid naive patient and diversion abuse -- but the fact that it is in a resistant pouch will indicate that it's different; the schedule I I

classification, the educational materials, the computer system, and the counseling programs.

We have what we call a quality assurance program which is really our vigilance program, and how we're going to monitor how this drug is used. There are a variety of surveillance programs that we will be using, including national databases such as the NDTI and the NPA which are programs that routinely track how drugs are being prescribed, who's prescribing them, what the diagnosis is.

And through looking at this in a quarterly basis and an annual basis, we can determine whether inappropriate clinicians are prescribing *Actiq*™.

Our adverse event reporting system is a system that alerts us if there are any adverse events that are being reported and whether the product is being used correctly in those adverse event situations. The off-label use is something that can be picked up in the databases that I mentioned -- the adverse event reports that I mentioned -- but it also will be picked up in our monitoring of our sales.

We will be able to tell where this product is being sold, which wholesaler is sending it to which pharmacy, which pharmacy is sending it to which physician, and if there's any indication of off-label

use we'd be able to pick it up pretty quickly.

Accidental exposures will be picked up through the adverse events system and also through communication with our medical communications group. The issue of diversion and abuse, we will be relying on the current systems. This is not something that we believe will be a major issue for this product.

But with all of these surveillance programs we will be doing continuous audits and making adjustments as necessary to labeling educational programs, and we will be also monitoring very closely the promotional activity of our sales force to make sure that they comply with how this product is to be detailed.

And just to give you an example, if it's determined that *Actiq*™ has being used for post-operative pain, for example, we would be very quickly able to identify the sites of possible misuse by going to the drug wholesalers, finding out where they have sent it, to which physician.

And that finding those physicians maybe are surgeons or not Hem/Oncs or cancer specialists, and we will contact those that we have identified as possible misusers of the product, and will reinforce the indications and contraindications for the product and

this again, to re-emphasize that the treatment of post-operative pain would be a contraindication for this product. And we will provide additional follow-up as needed.

Any time we become aware that there is a possible misuse situation, we will be sending a SWAT team, if you will, into the area to determine what the problem is, who is misusing it, why it was being misused, and initiate whatever steps is needed to make sure that this situation is corrected.

We will even, if we identify a group that are using this inappropriately who should not be using it or who do not agree to abide by the way that it's being designed to be used and labeled as such, we will even refuse to sell or to distribute the product to those people. We will do whatever it takes to make sure that this drug is used as indicated.

So in summary, Abbott and Anesta are committed to executing an innovative Risk Management Program that really goes beyond any other risk management program that we are aware of. And the goal of this Risk Management Program is to protect the availability of *Actiq*™ for cancer patients who do need it, and strongly deter product misuse.

And I believe Steve, you're going to

summarize.

DR. SHOEMAKER: As a final summary, what I would like to do now is give you an idea of what our position is on the questions that have been presented to you by the FDA. The first issue is, does the expected benefit and the intended clinical population outweigh the risk of accidental injury inherent in this product? And we think the answer is yes. Clearly, breakthrough pain represents a large, unmet clinical need, and *Actiq*™ has been proven to be effective and safe in meeting this need.

We also believe that it's very important to have a risk management program, and we've developed a program that provides aggressive safeguards to reduce risks in three major areas: accidental injury to children, misuse in opioid non-tolerant patients, and also addressing the risk of diversion or abuse.

Next question was whether the clinical effect demonstrated in 200/013 -- now, this was the trial where there was an open titration followed by the placebo comparison to OTFC in a blinded fashion -- was the clinical effect there -- does that represent a significant clinical effect? And we believe that it does.

For example, when we asked patients to rate

the global performance of OTFC at a time when they could integrate both the analgesic effects and the potential side effects, these patients were telling us that OTFC performs significantly better than placebo. And in addition, in the open label comparisons when we asked them to make that same comparison with their previous breakthrough medications, again, with highly significant P values, OTFC was rated better than their usual medication.

In addition, when we look at patients who are eligible to enter the long-term safety trial, 92 percent chose to continue on *Actiq*™ and not return to their usual breakthrough pain medications. Now to be fair, we were giving them *Actiq*™ and they didn't have to pay for it, but in addition, we did ask them to fill out diaries once a day and they had to be in contact with their physicians at least once a month.

We've demonstrated that the speed of onset is rapid, and we feel this is an important advantage in treating breakthrough pain. And we also believe that in study 011 -- this was the titration blinded trial in the patients on oral opioids -- that we do have evidence in this controlled trial of a dose response.

Another question was whether the sponsor has

adequately identified a rational approach defining the appropriate dose. Now, we realize that the titration screening that we outlined in the package insert is perhaps not as clear as it should be. What we'd like to do then, is have you consider a revised scheme.

Now, the goal of this titration scheme is to determine the minimum effective dose that provides safe and adequate analgesia using a single unit. So this approach is similar to the one that was studied in the 013 trial.

In other words, everybody should be started at 200 micrograms. If you take this initial unit and you don't get adequate pain relief after 15 minutes -- 15 minutes after you've finished consumption -- consumption takes about 15 minutes, wait another 15 minutes -- you should achieve the maximal effect.

If you haven't achieved adequate pain relief you could take another unit and you could take up to three units. Now, if you find that consistently you need more than one unit to treat an episode, then you would go to the next higher dose.

For example, if you were at 200 you would go at 400; if this happened at 600 you would go up to 800. This then, is the scheme that we would recommend.

And finally, the question that 's been posed is whether the sponsor's Risk Management Plan is adequate. Well, we feel that this plan provides aggressive safeguards to prevent inappropriate use. And again, we're specifically addressing issues related to accidental access by children, the use of opioids in non-tolerant patients, and to address the issue of the risk of diversion or abuse.

Again, we feel that the benefits of *Actiq*™ outweigh these finite risks and we believe that we must keep these cancer patients in mind. We must remember that these patients are living at home, often experiencing severe pain, and we believe that *Actiq*™ should be made available consistent with other potent opioids that are already in the home.

Well, with that, that ends our discussion. Thank you.

CHAIRMAN DOWNS: Thank you. Let's take a -- I'm going to shorten the break period to ten minutes since we're pretty well behind schedule now, and I will ask that everybody be prepared to be back here in ten minutes; that will be at a quarter-till-the-hour according to my watch. I'd like the members of the committee to please consider any questions you might have as soon as we return. Thank you.

(Whereupon, the foregoing matter went off the record at 10:35 a.m. and went back on the record at 10:47 a.m.)

CHAIRMAN DOWNS: I'd like for the committee at this time to consider questions for the sponsor. The sponsor, especially the speakers this morning, would be prepared to come to a microphone that's accessible, I would appreciate that.

Members of the committee, do you have questions of the sponsor? Dr. Palmer?

DR. PALMER: I was wondering about the labeling -- if the patient labeling and instructions have been rated in terms of what kind of grade you have to be able to read at in order to comprehend the labeling, especially the pouch labeling; and whether or not there's been any consideration of some sort of symbolic labeling as well as the print labeling to address the question of people who really can't or don't read.

CHAIRMAN DOWNS: A sponsor, someone to respond? Dr. Callan.

DR. CALLAN: Yes, Dr. Palmer. I'm Clair Callan from Abbott. We do plan to make sure that this patient labeling is understandable at relatively low grade level, probably. We have not yet tested it,

it's not final, but we will take steps to ensure that this can be understood by any patient that is likely to be using it.

And we have considered the use of graphics as you suggested, but again, no final decision has been made on that yet.

CHAIRMAN DOWNS: Yes sir?

DR. ROTHSTEIN: Dr. Rothstein. Could you define for me a little better what a child-resistant pouch is. Has this in fact, put -- have you gone to a day care setting to see how long it takes for a group of kids to open it and what tools they need? The reason I'm asking, this product -- at least theoretically -- has the ability to change the epidemiology of childhood poisonings.

Since most childhood poisonings tend to be toddlers, tend to be picking up pills or being fed pills by siblings. This now has the potential to at least, open it to an older group of kids. At what age can they get into the packet and what do they need to do it?

DR. GOOD: Yes, this package was tested -- I'm sorry, I'm Steve Good with Abbott. The packaging was submitted to Associated Testing Labs which is an approved agency of the Consumer Product Protection

Agency. It was tested against the Poison Prevention Act, 16 CFR 1700, and it did pass. And children up to the age of four were part of the study.

DR. ROTHSTEIN: Can you translate that? What is 16 -- how long does it take a child to open it? Can a 2-year-old open it; can a 6-year-old open it?

DR. GOOD: Well, they're instructed -- in the first five minutes they're asked to open the package. Then after the first five minutes they're shown how to open the package with scissors but they're not given scissors. They're told that they can use their teeth.

UNIDENTIFIED: Can you see this to describe this data?

DR. GOOD: Yes. Down in the area of the 200 children tested, that's part of the protocol, the first five minutes there were two failures, which is still within the acceptable limits. The second five minutes they are shown how to open the package with scissors; again, they're not given the scissors to open it. And this is tested in day care centers.

DR. STRAIN: This is Eric Strain from Hopkins. If you could just clarify, what's the age range? What are the age of the children that are

doing this?

DR. GOOD: Up to, I believe it 's 51 months. I can double-check that.

CHAIRMAN DOWNS: Yes?

DR. McNICHOLAS: Laura McNicho las, I'm also with the Drug Abuse Committee. Do you have any data on the patients who were in, for instance, the long-term study, who opened the pac kages prematurely? For instance, they didn't want to have to worry abou t finding the scissors or whatever, when they ha d breakthrough pain, so they kept two or three of them open?

DR. SHOEMAKER: We don't have any evidence that that occurred in our trials. Maybe during th e break we can check with some of our investigators to see if they know anything about that. But that wa s not reported in any of the patients in the trial.

CHAIRMAN DOWNS: Dr. Ellis.

DR. ELLIS: John Ellis, Chicag o. In follow up to that, I wonder if, when people have to pay for this, if they will manage it differently; that is , patients from the way it's recommended. If peopl e will choose to use -- if the 1600 micrograms cos t twice what the 200 micrograms, I could see physicians saying, get the 1600 and lick it twice, sort of thing

I wonder about.

And then having remnants around more likely based on how the pricing is done. Because I imagine in these trials people are given the medication free of charge and probably very responsibly able to get whatever dosage was necessary.

DR. SHOEMAKER: Yes, I understand your question. That's a very important consideration, and although the exact pricing scheme hasn't been determined yet, we want to ensure that there are not incentives to prescribe a higher unit and to partially consume that unit. So the higher doses will be priced higher than the lower doses.

DR. PATT: I'd like to make a comment. I'm Richard Patt, M.D. Anderson Cancer Center. I would say that patients were very concerned about child safety, and I think if there's a tie, and if patients understand that following the instructions mean better safety, that they will follow the instructions.

CHAIRMAN DOWNS: Down at the end someone had their hand up.

DR. RAGHAVAN: Derek Raghavan, Los Angeles. I'd like to ask a detailed question about the conduct of the trials. Looking through the participants to the various trials, it looks like between 30 to 40

percent of your investigators only entered less than three -- three or less patients.

I'd like to ask, what do you think that's done to the quality of the data, recording of side effects, following the protocol?

DR. SHOEMAKER: Well, first of all I'd like to point out that doing this type of trial is very difficult. We were trying to recruit patients who are concerned often about other things going on such as active treatment of their cancer, and we had to exclude patients that were undergoing active treatment because that would have affected their pain scores.

So first of all we had to have patients who had moderate to severe pain, that were relatively healthy during the initial phase, so they could fill out diaries. So it was very difficult to recruit patients which is why we had to use a large number of sites.

And I don't know, this may be typical of what happens in some cancer treatment protocols, where actually there's sometimes so few patients that sometime sites only recruit one or two per site. But again, the fact that there's a lot of sites relates to how difficult it is to do this type of trial in an outpatient environment.

Dr. Portenoy, maybe you could add from your experience as a pain researcher?

DR. PORTENOY: I'm Russ Portenoy. I would just add -- just reiterate what Dr. Shoemaker said; that it's very common for that to happen in multicenter, analgesic trials; that a portion of sites will enter very small numbers of patients because of the difficulty involved in recruitment.

CHAIRMAN DOWNS: Ms. Curll.

MS. CURLL: I do have a question. I was looking at your numbers and it appears that the numbers are not representative of the population at large, and I'm referring to ethnicity. Your number of Blacks and Hispanics are not very well represented and I was wondering if you could explain that to me.

DR. SHOEMAKER: Well, I think that's an unfortunate occurrence. Again, it was very difficult to recruit these patients. What we ended up is taking a combination of approaches, by going to the large cancer centers such as M.D. Anderson and Memorial Sloan-Kettering, in addition to busy, private practice centers. And this is how the data turned out. Fortunately, some of the other trials such as the acute pain trials where we were studying the pharmacology, we did have a better representation.

MS. CURLL: You're saying priv ate practice?

DR. SHOEMAKER: Yes, some of t he sites were private practice. Again, because you need t o understand that the majority o f these cases are being treated as outpatients.

CHAIRMAN DOWNS: Yes sir?

DR. RAGHAVAN: Derek Raghavan, Los Angeles. Back to Dr. Shoemaker. I'm so rry, I don't want to be picky but you didn't answer my question; you jus t apologized for the fact that you used a number o f different investigators. I understand these studies are difficult. My question was, what did you do t o ensure quality of data?

Did you have investigator's meetings, di d you have educational programs? What did you do t o maintain the quality of the data given the fact that you had to use the mechanism of getting multipl e investigators, some of whom di dn't put a lot of cases in?

DR. SHOEMAKER: Sorry about that. Maybe I didn't understand it correctly . But yes, we did have exte nsive investigator meetings ahead of time. W e also included things like pati ent education videos to make sure that we were giving uniform instructions as far as h ow to fill out the diary, when to start th e

clock when you took your medication, how to report your adverse events, and so on.

So those were kind of the ways we tried to control for this problem of the difficulty of recruiting patients.

CHAIRMAN DOWNS: Yes sir?

DR. MAX: Mitchell Max. I have two safety questions. The first is regarding childproofing; 6- and 7-year-olds are pretty good with scissors and are interested in lollipops. Is there any comparisons or any data about say, the child-resistant twist tops? After what age those are safe and prevent kids from getting in the -- would that be an alternative -- a favorable or unfavorable alternative to this sealed thing? Of course a twist top, once you used -- you could put a partly-used Oralet back in it.

DR. SHOEMAKER: See if I understand your question correctly. It's whether it's relatively more difficult or easier to cut a pouch or to twist the cap off a pill bottle?

DR. MAX: For an older kid who can use a scissors, what's going to be safer?

DR. SHOEMAKER: I do not know the answer to that and I don't know if any of my colleagues from Abbott who deal more with packaging issues would know

the answer.

DR. MAX: Okay.

DR. SHOEMAKER: I think that's unknown.

DR. MAX: The second question I have is about the stiff chest syndrome. I'm a neurologist but my anesthesiological colleagues talk about this phenomenon when you get an IV dose of Fentanyl sometimes people can't breathe, they get a stiff chest, it's very hard to ventilate them. And that sounds like a scary thing to happen.

Could one of your experts in this comment on, at what doses it's been seen? I notice that this was reported with -- in the earlier Oralet trials in one subject. Tell us about this phenomenon.

DR. SHOEMAKER: I'd like to let Dr. Stansky answer the question, but before he does that I want you to remember that the cases that occurred in the earlier studies, the chest stiffness was only seen at the time of induction of anesthesia, when the patients were losing consciousness and they were receiving other medication.

There has been no reports of chest stiffness in somebody receiving just OTFC who's not about to undergo anesthesia. And in our earlier studies I know there's small numbers of "n's", but we gave doses up

to 5 milligrams to normal, volunteer anesthesia residents who did not develop problems with chest wall stiffness.

But maybe Dr. Stansky would help us a little bit out with some of the pharmacokinetic dynamic issues.

DR. STANSKY: Don Stansky from Stanford. I served as a clinical pharmacology consultant for this product since it was first conceptualized. I think Mitchell, the key thing is the rate of plasma level increase; that with IV bolus injections where you have a very high peak concentration and then rapid movement of the drug into muscle tissues, the rigidity is reality and most anesthesiologists are aware of that and treat it.

With this product here, the rate of absorption is such that your plasma levels increase slower and the rigidity has not been seen as an issue to the same degree, because it's equivalent of a slowish infusion. And also the -- and so that in the clinical studies where there's no other adjuvant drugs being given, rigidity has not been an issue. Respiratory depression can be -- in other words, as the plasma levels increase -- but the rigidity that we typically see with IV bolus has not been seen here,

and I think it's the rate of drug concentration increase.

DR. MAX: So you're saying this is a muscle or local muscle phenomenon, and the other thing --

DR. STANSKY: Well --

DR. MAX: -- what's the lowest dose of Fentanyl IV this has ever been clinically --

DR. STANSKY: There's a combination of both central and muscle and probably some spinal cord components. And frequently in clinical anesthesia, there's multiple other drugs that are interacting there that can be a component of it. Whereas here there would be only the one drug.

CHAIRMAN DOWNS: Dr. McCormick?

DR. McCORMICK: I wonder if we could elaborate a little bit more on this? I guess I was thinking along the same lines. There were a number of patients in these studies report with -- a small number, albeit -- with hypertonia. And I wonder if you could explore that with us a little bit.

DR. STANLEY: With mu-acting opioids --

CHAIRMAN DOWNS: Dr. Stanley.

DR. STANLEY: Dr. Ted Stanley from Anesta. With mu-acting opioids it probably related to the rate at which the drug gets into the brain and spinal cord

that determines whether rigidity is going to occur.

Morphine as an example, given intravenously at any dose, just doesn't do it -- doesn't get into the brain fast enough because it's not lipid-soluble enough. With very lipid-soluble drugs intravenously, this becomes reality.

You can see it with Fentanyl, and su-Fentanyl, and al-Fentanyl, or remi-Fentanyl. Not really very possible with Morphine; you can't ever say impossible. With Fentanyl given oral transmucosally, again it's the rate, and it doesn't get in.

Now, when any patient has an opioid systemically on board and another drug is used to produce unconsciousness, be that an intravenous drug or an inhaled drug, oftentimes at the time the patient is losing consciousness there is a stiffness that can be detected. This occurs with Nitrous Oxide and Morphine as well. But it's about the time of loss of consciousness that this can occur.

Since even 5,000 micrograms of OTFC -- which is a huge dose -- in ten volunteers which was originally studied 12, 14 years ago does not do this, it would be very, very rare if any dose that is being approved -- or considered for approval -- could possibly do this, unless another induction anesthetic

agent was used concurrently.

CHAIRMAN DOWNS: Dr. Young?

DR. YOUNG: I have two questions. The labeling information we were given appeared vague regarding use in pediatric patients, and your studies were limited to, I think, patients in their early 20s -- that was the lowest age. So I was wondering if you were going to be more specific about use of these drugs in the lay -- in younger patients, or whether you're going to say that it's contraindicated.

The other question I had was whether there was a need to have any flavor at all associated with this formulation? I understand it was an issue with the other Fentanyl transmucosal product for premedication and sedation. But for this one, is there a need to have it flavored at all?

DR. SHOEMAKER: Well, maybe I could address your first question about children, first. Actually, the history of OTFC is interesting because in our first set of clinical trials the vast majority of the patients were children and they were opioid naive children. And in those studies we were able to determine that the pharmacokinetics were similar to what we see in adults.

Now as it turns out, in our chronic pain

studies we did not enroll children. I think cancer pain is a problem in children; unfortunately it's not as well understood. As Dr. Weinstein pointed out this morning, a lot of the pain is treatment-related, it's procedure-related.

And actually, we have that indication now, and OTFC has been used to premedicate before bone marrows and lumbar punctures in kids with leukemia, for example, who continually have to be staged -- again, in a hospital setting, in a monitored anesthesia care setting.

I think the one piece that's missing right now is safety data on children. If there are children that are opioid-tolerant experiencing chronic pain, we just do not yet have the safety data to make a statement. However, we do have this pharmacokinetic data from before and we do know what happens when opioid naive children are administered OTFC.

As far as the flavor issue, maybe Pam, you could help us out with that one.

MS. KEDZIERA: I'm Pam Kedziera. I'm a clinical nurse specialist that works in a pain practice at Fox Chase Cancer Center. We were a site for the study.

My job is teaching patients how to take

their medications, and one of the things I find nurses always challenge to do is how to get the patient to take it. And they often have to put medicines in other products to conceal taste.

This particular product has to stay in the individual's mouth for 15 minutes. It needs to be palatable to them. And oftentimes the other products that we now have available we find specialists and patients and families adding to puddings, adding to other substances to conceal that taste.

I think the taste is important. They may be using this four times a day. It's not a one-time event over the course of their illness, and since it will be a part of their life I think it is important to make it palatable to them.

DR. HEDEN: John Heden with Abbott. I just want to add one other comment to the flavor issue. This was a key thing that we balanced as we were looking at this product in its development. We obviously understand the issue of attractiveness to children, and certainly with the *Actiq*™ product versus the Oralet product, made a conscious decision to change its attractiveness, eliminate a red color to it to minimize its attractiveness to children.

One of the things that the committee should

realize is that the drug is suspended in a sucrose matrix. So even if we took the minor amounts of flavor that are there that make it palatable to the cancer patient, it would still have a sugar taste to it; it would still be sweet.

So our balancing was, let's make it as unattractive as we can and eliminate -- and make it as palatable to the cancer patient as we can, but there would still have been a sweet taste to it even if we'd eliminated the flavor.

CHAIRMAN DOWNS: Dr. Horlocker?

DR. HORLOCKER: I'd like to ask a little bit about respiratory depression. Certainly, in your post-operative patients there were patients that had hypoventilation and desaturation, and yet in the chronic pain patients, no effort was made to monitor by pulse oximetry. Really, the only monitor we had of potential respiratory depression was the report of somnolence. So how can you definitively say that you have assessed that safety factor?

DR. SHOEMAKER: Well, I guess there's always tradeoffs when you design clinical trials. We felt that it was very important to be able to do these trials in the patient's home, and for that reason we did not have pulse oximeters there. If we had to --

DR. HORLOCKER: There are portable pulse oximeters that are about the size of a diskman now, which are very unobtrusive.

DR. SHOEMAKER: A good point but again, sometimes you're limited in what you can do with these patients. But I guess the other question is, these patients are also on other opioids and these other opioids are causing sedation. But I think it's the clinical experience that tolerance to respiratory depression often develops.

But the other question is, what is the clinical significance of this respiratory depression? And I think we answered that question in that, patients did not get into trouble with respiratory depression.

Now, we took this issue very seriously. We had a group of four clinicians come in and look at every patient who had an AE related to their respiratory system, whether it was dyspnea or whatever. And also looked at patients who had the adverse event of sedation. And we looked at the doses they achieved, the maximum dose they used for an episode, and tried to figure out, could we find evidence of respiratory depression?

And perhaps one of those clinicians - -

either Dr. Walsh or Dr. Portenoy -- could comment. Because they participated in this, in addition to an anesthesiologist, Dr. Rauck, and a pulmonary specialist, Dr. Tom Petty from the University of Colorado.

Well John, maybe you could comment first.

DR. FARRAR: Okay. My name is John Farrar; I'm a neurologist at the University of Pennsylvania with a primary interest in cancer pain management. We were a site for conduct of the trial and enrolled 13 patients into the trial.

We need to remember that respiratory depression is a very clear and evident possibility in patients. On our service we see, probably once a month, patients who have difficulty with opioid-caused, respiratory depression. These are all opioid naive patients in our hospital setting.

In the outpatient setting we daily titrate people to very high doses of morphine and other opioids with monitoring on an outpatient basis, with caregivers and nurses. The use of this particular drug presented no additional difficulty in doing that because we were using opioid-tolerant patients.

We have found in accidental overdoses -- not with this drug but with other drugs; with Morphine in

particular -- that people can take five and six times the prescribed dose in a rescue circumstance where they're having intense pain or where they accidently take or forget that they've taken pills, without significant respiratory depression.

And by significant, what I mean is clinically important where they needed something done. And I think it's important to keep that in mind. The measuring of the saturation or to saturation, while it would be interesting from a pharmacokinetic and dynamic perspective, would not contribute anything additionally to 20 or 25 years of experience in treating patients with very strong opioids in the home setting.

DR. PATT: Richard Patt, M.D. Anderson Cancer Center. Just to reiterate some of that, I think there was an effort to mimic usual, clinical practice; which is commonly using high doses of opioids without special monitoring situations.

And I'd also point out that the pilot of care community has come to recognize that in fact, opioids are typically beneficial for patients with respiratory distress; that by slowing breathing a bit and increasing ventilatory efficiency that in fact, multi-symptomatic cancer patients generally breathe

better when using opioids than without, and they're often prescribed specifically to ease air hunger, even in patients without pain.

But I think the most important thing was that there was an effort mimic usual, clinical practice of outpatient pain management in cancer patients.

DR. PORTENOY: I'm only going to add one thing. I think it's a very important issues and in clinical practice treating patients who have cancer pain, the overwhelming majority of patients who are evaluated for so-called, opioid-induced respiratory problems turn out to have some other process going on. They have a pulmonary embolism, or mucous plug, or pneumonia, or another drug was co-administered.

And because of the concern that the AEs reported in this study may be hiding other issues, may not be clear enough, the company empaneled this group of us to go over every single record. And we did that, and in not a single case did this expert subcommittee find an AE related to the respiratory system that we could say was opioid-related, respiratory depression.

And I'm basically very secure that this drug, when used in opioid-exposed patients, is safe

from that point of view.

DR. WALSH: Declan Walsh, Cleveland Clinic Cancer Center; I work in the palliative medicine program there. I just want to support what Russ has just said about the review of these cases, number one. Number two, the generic experience in many thousands of patients is that when opioids, included Fentanyl, are used correctly, that respiratory is actually an unusual event.

And thirdly, I think it's important to remember that the indication that this product is intended for, which is breakthrough pain -- rescue dosing of these people with breakthrough pain -- that the existence of that type of pain in and of itself, is a stimulus to respiration and is likely to prevent any inhibitory effect of opioids in that setting. And that's a widely accepted principle in cancer pain management.

CHAIRMAN DOWNS: On the agenda you'll notice that we have two more periods for discussion later. We're well behind the schedule right now so I'm going to stop the discussion at this point and allow the FDA to proceed with their presentation. If you have questions of the sponsor please write them down so that you don't forget them, and we can cover those in

the next discussion period.

We'll proceed then, with the FD A presentation.

DR. DODDAPANENI: Good morning . My name is Suresh Doddapaneni and I am the reviewin g pharmacokineticist for this NDA at the agency.

Earlier, some pharmacokinetic data on this product was presented by Dr. Shoemaker of Anest a Corporation and in this short presentation I will try to bring out some additional points that were no t apparent in the earlier presentation.

Actiq™ is a lozenge on a stick and i s designed to be sucked by the patient so that th e released Fentanyl dissolved in the saliva is meant be absorbed through the oral mucosa.

However, in practice, some of the Fentanyl dissolved in the saliva is swa llowed and the systemic Fentanyl levels that you see after the use of th e *Actiq*™ are due to a combination of absorption through the fecal mucosa as well as in the gastrointestina l tract.

And as such, the oral bioavailability an d the systemic Fentanyl profile will vary depending upo n the fraction of Fentanyl that is absorbed in the oral mucosa and the fraction that is swallowed and absorbe d

in the gastrointestinal tract.

Now, in addition to the infancy, pharmacokinetic availability of Fentanyl, there is another level of variability that is unique to *Actiq*™ because of its unique mode of administration. In the clinical trials consumption times of the meds were used. And it becomes very important that the patient uses the right and consistent consumption techniques in terms of the consumption times, the second rigor, and the saliva swallowing frequency to minimize both the inter-patient and intra-patient variability.

For example, I think this point was brought out by Dr. Shoemaker earlier. If a patient chews the lozenge and swallows it immediately, most of the -- almost all of the drug is absorbed in the gastrointestinal tract, resulting in oral, lower bioavailability, lower peak concentrations, and longer times to achieve peak concentrations. In other words, this will approximate an oral solution.

On the other hand, if patients who sucks on *Actiq*™ relatively rapidly might have relatively higher peak concentrations and relatively higher oral bioavailability.

Dose proportionality data at single dose was also presented earlier, but that data was in the

graphical form and here I would like to present the same data in terms of numbers.

Both AUC and T_{max} increased in an approximate dose proportional manner at single doses in the range of 200 to 1600 micrograms. What I would like to point out here is that there seems to be quite a bit of variability in the pharmacokinetic parameters, especially T_{max}. Coefficients of variation seem to be quite high.

Now, these are mean values and median values would be -- are somewhat lower. Now, what this may mean clinically is that at least in some patients -- and especially in the titration case -- the peak effects may not be seen within 15 to 20 minutes after the consumption of the first dose, and the patients may proceed to consume another dose even before they realize the full effects of -- the full benefits of the first dose.

And the final point I would like to make is that if *Actiq*™ is administered repeatedly at very short intervals, there's a possibility that it can accumulate resulting in intolerable side effects. And in study -- I think it's 015 -- effort was made to find out if this was the case.

Although the data is not presented here, the

results showed that when *Actiq*™ was given repeatedly up to doses of 1200 micrograms every four to eight hours, there was no tendency towards accumulation. And unfortunately, data from this study was not available for the top dose, which is 1600 micrograms.

However, patients in other clinical trials did use this dose and reported that they did not have any unexpected or unusual side effects. Thank you.

DR. WRIGHT: I'm Dr. Curtis Wright. I would like to just say for the record that this is the third time I've had to follow Dr. Portenoy's presentation of the same material, and each time I do about half of my overheads go out of my pack. I'm going to limit my discussions to the things that I think you may want to consider about these clinical efficacy studies.

The clinical trials portfolio included the pharmacokinetic study in cancer pain patients that the pharmacokineticist just referred to: the two efficacy and potency studies in the post-operative pain model; the 013 study which is the placebo-controlled efficacy study; and the two titration studies.

It is important to note that a considerable amount of the statistical power of these clinical trials came from the fact that they were repeated dose studies. In the 92 patients who participated in the

013 study, they had a potential 644 active drug episodes and 276 placebo episodes.

As is usual in cancer pain studies, not all episodes actually occurred as planned. Seven patients withdrew early due to AEs, eight patients didn't use all ten units in 14 days, two patients were still running at the end of the study, one patient said, I simply prefer my regular rescue medication, a patient had to enter radiotherapy, one patient declined to participate, and a couple of patients consumed their units within two hours of a previous unit, thus making the data questionable.

Overall, the performance in the trial was quite good in a trial of this kind. Nine percent of the placebo episodes and nine percent of the OTFC episodes were unusual, did not occur, or were unratable in the course of the study. So the ITT evaluation was based on 227 placebo and 505 active treatment observations.

You've seen the results of that; I'm not going to repeat them. I will offer one point for consideration. Most breakthrough pain on average, lasts 30 minutes or less, and the claimed advantage of this product is that it has fast onset and rapidly achieves its analgesia.

Therefore, especially since most patients could use rescue in these studies after 30 minutes, the cogent time points are 15 and 30 minutes -- not out to 45 minutes or an hour.

This is a histogram that attempts to show what actually happened in terms of the subjective response for the patients. The striped bars are the placebo episodes; the black bars are the OTFC episodes. This is a very poor, poor, fair, good, and excellent pain relief.

And as you I think, can see, most of the placebo responses that contributed to the differences between the treatment groups in the trial, occurred down in the very poor and poor group. The fair, good, and excellent responses that were differentially seen for the OTFC, was responsible for most of the differentiation seen in the scores.

Looking at that a little deeper, we did some exploratory analyses, and this requires a little explanation. We defined fully successful as a two-thirds or better reduction in pain, and as less successful -- perhaps unsuccessful -- episodes that had a one-third or less reduction in pain. A simple categorical analysis.

Placebo success was seen most frequently

with the 200 and 400 -- as might be expected -- and fell off at the higher dosage strengths. OTFC success remained relatively constant across all the strengths. So a considerable portion of the difference between the two groups was seen out at these higher dosage strengths.

When you look at failures, placebo failure differentially, is seen at the higher dosage strengths as well; when you get down to the 200 and the 400 units there's not too much difference between the two treatments.

So that's what happened in approximately two-thirds to three-quarters of the patients who titrated successfully and were satisfied with the medication.

You should think about questions about what happened to the other patients, the people who were not successful. Some of them we know, they preferred their regular rescue, some of them we know titrated all the way up without achieving adequate analgesia using the unit, and they represent a significant proportion of the users.

These were descriptive titration studies. They weren't really prescriptive titrations. An individual could come in having used two 400s, have

their dose increased, and the next day they would use one 600 and actually have a substantially lower dose on the second day. It's a reasonable, clinical strategy but it muddies the data a bit.

I think you need to think about if a clinical practitioner using this "start low and advance slowly" paradigm will achieve similar efficacy results in clinical practice. We looked at the two titration studies with this in mind.

This is the same kind of analysis we showed before. The black bars are the percentage of patients who failed by dose, and the striped bars are the percentage of patients -- I'm sorry, the black bars are the successful, the striped bars are the failed patients.

And what this analysis shows is that as you proceeded in the trial, if you were successful your trial was over. As soon as you had two successful episodes at a single unit, you were out of the study. So the study showed that most of the success was seen by the patients at the lower dose early in the trial, and the patients who had difficulty being treated went out to the highest doses and had a fairly low margin of success rate.

Study 12, the study in which the patients

were on transdermal Fentanyl was similar. It doesn't mean that the big doses don't work. I think what it means is that for a clinical population that was fairly reasonably selected, that is typical of people who are not achieving adequate pain control with their drugs that they're taking, the marginal probability -- the likelihood that the next dose increase is going to do the job -- falls off as you get much above 800, 900, 1200, 1600. So there really is no apparent benefit of going to larger and larger and larger and larger doses, except in clinically-unusual or selected cases.

I agree with the presentation that was given this morning about the efficacy. There was an effect in the target population regardless of the type of ATC opioid analgesic used. The usual effective dose was in the 600 to 1200 microgram per unit range, with the smaller and larger doses being useful for titration and tolerance, respectively.

About one-quarter to one-third of the patients didn't get the results that they had hoped for from the use of this product. But I think that this is a population that didn't get the results that they hoped for in the use of conventional Morphine analgesia either.

I'd like to turn over to Dr. Kahn, who will discuss the safety.

DR. KAHN: Thanks, Dr. Wright. Good morning, everybody. Could I have the first slide, please? Thank you. I'm going to be also covering a lot of information that essentially has been discussed extensively by the sponsor, and also some of the questions that have been anticipated by the panel.

First I'd like to talk about the adverse events that were observed in the non-opioid tolerant population that was studied for this particular NDA. There were five studies of which the first three were normal volunteers who participated in pharmacokinetic or bioequivalency trials, and then there were also two studies in post-operative patients.

As Dr. Shoemaker said before, there were -- these were patients who were also receiving at various points in the trial, intravenous Morphine PCA. The adverse events that were seen are very typical for patients who receive narcotics -- opioid medications. These were the only studies in which monitoring of respiratory depression was conducted.

And hypoventilation in these studies -- particularly for normal volunteers -- was identified by a rather high hurdle. In order to be labeled as

hypoventilation as an adverse event, the patient had to have both a sustained desaturation to 85 percent and a respiratory rate less than six.

So that if the patient had a brief period of desaturation and was able to improve their saturation by verbal prompts to breathe, they were not defined by hypoventilation. In one study, patients were defined as hypoventilation if they had a sustained desaturation while on oxygen therapy.

In these studies, you can see in one study of normal volunteers there were not episodes of desaturations. In one study, four desaturations occurred -- and this was the only study where PC O_2 was measured, and 9 out of 12 patients demonstrated -- I'm sorry -- yes, 9 out of 12 demonstrated hypercarbia by arterial blood gases. And these were at doses of 800 micrograms.

The final study, 12 out of 12 patients experienced desaturation in the range of 200 to 1600 micrograms, the full dosage range that is recommended for this drug.

In post-operative patients the results were very similar: 17 out of 77 patients experienced desaturation, and 4 out of 15 experienced desaturation -- again, in the clinically-relevant dosage range.

So respiratory depression which was treated with verbal stimulation prior to administration of oxygen and resulted in improvement of the patient, was not defined as hypoventilation; rather, those patients had to have a sustained desaturation and also unresponsive to verbal stimulation. Again, in this study this is called hypoventilation; some of us might call this general anesthesia.

Actiq™ in all dosage strengths was associated with the risk of respiratory depression based on incidences of hypoxemia of 33 percent in healthy volunteers, and 23 percent in acute post-operative patients who were concurrently receiving PCA Morphine.

Now, this is very similar to the experiences in the earlier NDA for Fentanyl Oralet where of course, there was a large body of data accumulated, and our only data which was accumulated for the pediatric age group. And in that group of patients there were 730 patients studied, all opioid naive subjects, all in the dosage range that we are discussing today.

There were two cases of apnea, both in 3-year-olds. You can see the weights and the dosage, and while 300 -- approximately 300 micrograms is in

the lower dosage range for this product, you can see that it's a very large microgram per kilogram dose for children of this age -- 30 and 22 microgram per kilogram.

Similarly, for desaturations, 42 cases. There were 18 cases in the ages of 2 to 9 in this dosage range; 21 cases in the adult dosage range; and 3 cases in the older dosage range. I hate to say elderly because I'm rapidly approaching the lower limit of that elderly. In any case, a dosage range of 7 to 15 micrograms per kilogram is the normal, clinical dosage range for Fentanyl Oralet and also for *Actiq*™.

And five cases of hypoventilation, again in the pediatric age group, with 200 or 600 micrograms per unit dosage. Which represents for these children, a 14 to 25 microgram per kilogram dose -- approximately twice what would be a per kilogram dose chosen for therapeutic purposes.

And when these studies were done there were plasma levels obtained in some of the patients, and so we have this information. The episodes of apnea were associated with a peak plasma level of about 4.3 nanograms per ml. You can see hypoventilation and desaturation, the mean -- these are mean peak plasma

levels.

For desaturation however, which is at 2.87 nanograms per ml, in fact half of those patients were lower than that, and their peak plasma levels were in the range of 0.7 to 2.8 nanograms per ml; again, from the pharmacokinetic data that we have it is possible to see a peak plasma level of approximately .7 to one nanogram per ml with a 200 microgram per unit dose of *Actiq*™.

Now, these are the demographics for the studies that were done for this NDA. Again you can see -- Dr. Shoemaker has gone over this information -- and since the study number 014 were patients who were recruited from the other studies, the demographics of course, are very similar.

Something that hasn't been mentioned before was that there was an attempt to classify the type of pain. And you can see that 80 percent of the patients approximately, had nociceptive pain, and 19 to 21 percent -- 20 percent approximately -- had neuropathic pain.

There was a desire to find out of there was any difference in outcomes for these categories of patients, or differences in adverse effect. And for virtually all of the adverse effects that were seen,

there were differences.

There was a slightly increased incidence of CNS side effects in the patients who had neuropathic pain. That may or may not have any significance; that may just be an implication that these patients required higher doses because -- based on prior experience many of these patients don't respond to low doses of opioids no matter what drug you choose.

And these are the common, adverse, drug-related events. Drug-related I want to emphasize, was as determined as Dr. Shoemaker explained, this was an attempt to correlate the observation of an adverse event with a temporal relationship to the administration of OTFC.

It's very difficult in a cancer population to say that -- who have ongoing disease, who are receiving multiple medications -- that there is a true and representative relationship. And of course, they are also on other opioids.

And clearly, this is a list that represents the expected opioid side effects. There were two accidental injuries that were thought to be related to *Actiq*™ use. These were both patients who became, perhaps a little bit dizzy or a little bit confused. One spilled coffee on herself and the other one

injured herself by, I think, a fall.

And in the chronic use patients, I'm referring to the short-term uses -- the dose titration studies and the chronic use patients are the patients in study 14 who were on therapy for 4-month blocks at a time which was the long-term safety study.

There's really no difference in the incidence of adverse effects that is worth commenting on. There were two episodes of myoclonus, out of a total of three in this study, that were observed and felt to be related to OTFC. And Fentanyl in any method of administration is known to be associated with myoclonus.

Now, going through the adverse events by body system, this is the total, comprehensive review that was given to us. Again, the attribution is based on the sponsor's attribution based on their interview of patients and their experience of adverse events and the temporal relationship to the administration of OTFC.

And you can see that most of the problems that were reported are digestive system -- that's nausea, vomiting, dyspepsia, things that you would expect from opioids -- and CNS which is dizziness and confusion, headache, somnolence. Somnolence of

course, as Dr. Shoemaker also pointed out, was a very prominent side effect.

The five cases that were reported as respiratory were four cases of dyspnea and one case of sputum production which probably has nothing to do with *Actiq*™. Dyspnea as an event associated with opioids as we've been discussing already, is a little bit of an unusual association. And again, it's very difficult to say whether there is in fact, a relationship to this drug.

One of the things that I had contemplated in discussing this drug and in my review, was whether these episodes of dyspnea may represent something that was brought up earlier -- possibly chest wall stiffness, possibly transient pulmonary edema, possibly episodes of hypoxia.

There's really no way to identify that without further information which has to be obtained by monitoring at the time that these patients were seen. And of course, that wasn't done -- that couldn't be done.

Everything else is not very important. The one episode of tachycardia is probably not related to OTFC.

So the number of patients with -- I think I

can probably skip this slide; it's basically the same information -- 53 out of the 149 patients who had adverse events were ascribed to be treatment-related; 30 out of 143 were considered moderate or serious; and 5 out of 86 were considered serious and were considered -- out of the 86 treatment-related rather, were considered possibly related to *Actiq*™.

There was one overdosage reported to us. It's an interesting case. A patient who was a 75-year-old man who was supposed to be taking the 200 microgram unit for his pain and was also taking transdermal Fentanyl -- 75 micrograms which was later increased to 100 micrograms -- and due to a pharmacy error he was given the maximal unit, the 1600 microgram unit, and took this for nine days for all of his episodes of breakthrough pain, and then the error was discovered.

In fact, the gentleman was fine. He had some behavioral changes. The investigator felt these were unrelated to *Actiq*™ but I would be very suspicious of that. But he didn't become apneic and he didn't have any other serious events.

Deaths in the trial were really due to progression of disease. These are patients with advanced cancer receiving palliative treatment;

metastatic cancer. In general, the withdrawals in the long-term study and all of the deaths in the long-term study were patients who were hospitalized for complications or progression of disease, and were off of OTFC at the time of hospitalization.

So there really was no temporal relationship between the period of time that the patient progressed most acutely while in the hospital and progressed onto death, and the use of OTFC. These patients were using OTFC only while they were out of the hospital.

One patient in this study, Dr. Shoemaker really discussed him much more extensively than I will now, who had progressive dyspnea and died on the way to the hospital. And this was considered possibly related to *Actiq*™ because he had taken his last unit about one-and-a-half hours before. But my feeling is that there is no causative relationship between these two events.

Now, as has already been alluded to and discussed to some extent, the only information we have about respiratory depression is in the acute, non-tolerant population and not in the chronic population. There was no monitoring in the studies of the chronic patient population and it's very difficult to have incidents of hypoxia or incidents of hypoventilation

reported in such a study since these are not self-monitored events.

Certainly the incidents of somnolence is of concern because we know that somnolence is associated with respiratory depression with Fentanyl and with other opioids, but particularly with Fentanyl the therapeutic serum level of Fentanyl associated with a -- rather, a therapeutic effect -- will also be associated with a 50 percent reduction in PCO_2 response.

I feel a little embarrassed speaking about this in front of Dr. Stanley because I and every other anesthesiologist in the country read this in his chapter in Miller. So you'll forgive me.

Tolerance to the respiratory depression effect of Fentanyl however, with chronic use has not really been established. Whether there is partial tolerance or complete tolerance simply is not known. It's possible there's partial tolerance but certainly complete tolerance is not studied at all.

On the other hand, in this group of patients -- many of which had a significant degree of respiratory impairment because of their disease, there were no episodes of apnea reported in this series.

In conclusion, I would like to offer the

following for consideration. The risk of respiratory depression is definitely established in the non-tolerant population; we know that. The risk and the nature of respiratory depression however, has not specifically been ruled out for the chronic population with the current data.

Other adverse effects that were seen in these studies are characteristic of Fentanyl and other opioid agents. Somnolence, dizziness, and confusion which had a fairly high incidence in the long-term study population, warrants special consideration in an at-home, unmonitored environment, both from the standpoint of patient safety and also from the standpoint of what we've already been discussing as disposal mechanisms for this agent.

Are patients who will become sleepy, dizzy, have to lie down, going to also be able to quickly dispose of the unit safely after they have used it?

And finally, the risks associated with accidental exposures, we've been discussing that already, and that is essentially the same as the risk that's seen in the non-opioid tolerant population, whether we're talking about children or adults.

Thank you.

DR. KLEIN: The abuse liability review is

really the prelude to the risk management plan which will be covered by Dr. Wright. The sponsor has suggested and asked that the drug product remain as a schedule II narcotic. With its status as a schedule II narcotic you essentially create a closed system of distribution with all sorts of anti-diversion regulations that are attached to it. And the closed system goes from the manufacturer to distributors to the health care provider.

When the drug gets to the patient there are dispensing limits in which no refills are allowed and the prescription can only be written. There is no limit on the size of the prescription however, although I presume that excessive prescribing by one physician to many patients would raise certain red flags with the Drug Enforcement Administration that would probably lead to some further investigation.

In addition, through estimates of medical use that we provide on an annual basis to the Drug Enforcement administration, manufacturing quotas are set for schedule II drugs.

Now, these are the actual, annual aggregate production quotas, the amount that has been produced in the United States from 1986; about 5 kilograms annually, through the 1997 projection of close to 200

kilograms. Prior to '86 the annual quota was in that same range, of 3 to 7 kilos on an annual basis. The big increase occurred in the early '90s with the approval of Duragesic.

Now, I have to apologize for not including this slide and the next slide in your handouts because I just received approval late yesterday from IN S America to present their data. But this is the prescription data comparing the retain sales of Duragesic, the Fentanyl patch, to the other Fentanyl products which are available.

And also, of course that doesn't include the total used in health care. A different source of data, the amounts of drug product that are sold to hospitals show where the injectable product are used predominantly over Duragesic -- although Duragesic is still used in the hospital setting.

Looking at the Medwatch data for the different products of Fentanyl you see that the major contributor is the prescriptive product, Duragesic, which is available at the retail level where we have over 2000 cases reported to Medwatch.

And for some of the other Fentanyl products -- I have to say that the second category of Fentanyl is kind of a conglomerate of not that well defined

cases, and this is always a problem with these sort of data systems. So I put that separately. It could very easily have fallen into the other categories as well.

But Duragesic was clearly identified in over 2,000 Medwatch cases, and Sublimase for instance, which is clearly identified by name, had approximately 287 Medwatch reports. I also want to emphasize that the Duragesic reports were primarily within the five -- past five or six years, and Sublimase reports go back to the '70s.

Now, we use the Medwatch Report really to indicate whether there's a problem. It's just another data gathering device that we use to indicate whether there's abuse or some outstanding problem with the drug.

And we lump terms together which we call neurabuse co-starts, which includes overdose, drug dependence reports, withdrawal syndrome, tolerance -- to give us a feel for what sort of abuse might be encountered out there. And we have over 200 reports for Duragesics, and for the injectable products, 62. And again, the 200-plus reports for Duragesic was over the past five or six years.

A percentage such as it is, is 1.2 - -

approximately 1.25 adverse reactions for neurabuse per 1,000 prescriptions. For Duragesic, for the take-home product versus the injectable product of approximately .6 adverse reactions per 1,000 prescriptions.

And finally, we'd go into some case reports and I was specifically looking for some sort of antisocial behavior and looking for the unusual type of events that are sometimes reported to Medwatch where a product is abused -- clearly abused.

And described -- where we have individuals who chew the patches and subsequently died; an individual who extracted the products from the patch and smoked it in the pen cartridge; and other individuals who obtained it from friends, that other sorts of unusual things.

So there were always those patients who manipulated the products because they weren't getting adequate pain relief from the patch. Or they'd stick pinholes in it or other things of that sort; rubbing it to try to get more Fentanyl to be released.

As a conclusion I would say that we're definitely seeing a different scope of abuse, different sort of problems with abuse of Fentanyl. Prior to approval of the prescriptive product Fentanyl was primarily abused by the health care practitioner,

but now we're seeing many more types of events.

Dr. Wright will describe the Risk Management Plan.

DR. WRIGHT: This is the problem as we see it. This appears to be a potent, opioid analgesic which appears to be of acceptable risk in the targeted clinical population. It also looks sufficiently like an item of candy, such that a young child might be injured or killed by an accidental ingestion. That's got to be dealt with.

In thinking about our experience with transmucosal Fentanyl, we have two ends of a risk continuum: the pre-operative or pre-procedural use by an anesthesiologist or similarly trained health care provider, which appears to be extraordinarily safe.

The experience with Oralet, despite our misgivings, was that used as directed and as it is used, it has done very well. We think that the outcome for a child who is found by the mother, cyanotic, is likely to be poor. But in between, you have a number of things that we consider to be off-label risk.

A child with an unwrapped unit in their hand; a child with a wrapped unit in their hand trying to get it open; the abusers that Dr. Klein just talked

about, with units wrapped or unwrapped; a prescription for a non-tolerant acute pain patient; a prescription for an unselected chronic pain patient; a prescription for an unselected opioid tolerant cancer patient; a prescription for an opioid tolerant cancer patient on ATC opioids, which is the indication; and conditions under which this product is dispensed in a hospital or hospice or other health care environment.

Can the risk of accidental or iatrogenic toxicity be reduced to a level where the benefits to the intended users outweigh the risk to the rest of the patients and the public?

The plan that's been put forward that you received in your package, has five elements: control of promotion, prescription, and distribution; warnings to all parties; specific instructions; surveillance; and intervention.

Promotion is intended to be restricted to pain and oncology settings; indications as a second line drug in the ATC population; restricted distribution through limited wholesalers; restricted prescribing -- very heavy patient selection criteria in the package insert; restricted dispensing through the pharmacy program previously described; and a potential -- although I believe this is still

something that needs to be seen if it's possible -- restricted reimbursement.

The warnings are the detailing programming that was discussed earlier; the box warning; the carton warning; the software flags in the dispensing software in the pharmacy; the pouch warning; the PPI; and caregiver-specific warnings.

The instructions: keep the unit pouched until just before use; destroy partially used units immediately; think about poisoning prevention at every step of the prescriptive process; and although the sponsor has not yet agreed to this, we think some emergency care instructions on the patient package insert on what to do if there is an accidental ingestion, would be helpful in an era of declining poison control center accessibility.

Surveillance plan is to watch for use by the addict community; watch for abuse by health care professionals; monitor off-label sales, predominantly through sales marketing data; look for adverse events, both in the medical literature and in the open public literature; and look for mis-promotion in the media or on the Internet, which is emerging as a place for remarkably fanciful information about pharmaceuticals.

The intervention program are targeted

physician intervention materials intended to be provided to an outlier prescriber; phone calls to outlier prescribers if the materials don't work; and if there appears a systematic problem, targeted educational programs for State Board and professional societies.

The agency review comments, as always -- what a lovely proposal, now where is your plan? There's a need for specific performance parameters: how often; how frequently; by whom? The need for reporting requirements: when will we hear about this, once a year or once a quarter, and through what medium will these come in?

And I think more important than the first two -- although the first two are important -- is, what are the triggers to the next action? You saw earlier that we count numbers -- we count numerator data when we deal with adverse events. How many near poisonings, how many accidental ingestions, how many episodes of off-label use?

But how do we deal with the denominator? Is a product that has, from a public health and from a regulatory perspective, 200 episodes in two million uses any different from a product that has 100 episodes in one million uses? That's not a facile

question to answer.

And I leave you for the risk management plan, for your perusals over lunch or whatever comes next, Mr. Chairman: Does this plan lower the risk to a level where the potential benefit to the patient outweighs the risk of iatrogenic misuse and accidental toxicity?

CHAIRMAN DOWNS: We have one more discussion from the FDA, correct? Chemistry?

DR. WRIGHT: No, I think we're done, aren't we?

CHAIRMAN DOWNS: We're done? Okay. We now have then time -- I'd like to thank the FDA for bringing us back closer to schedule. And we now have time for committee discussion. I'm sure the sponsor would like to respond to some of what we've just heard, but what I'd like to do is get back to the panel discussion first and then I'm sure there will be time for the sponsor to respond -- both through answering questions from the committee and also respond to the FDA.

Yes sir?

DR. MAX: Some potential users will have mucositis or other oral ulcers. Is there any information on kinetics? Is it just whether a

dangerous level of increased absorption might occur?

DR. SHOEMAKER: We have not to this date, studied patients for severe mucositis, and that is something that we plan to do, to just specifically answer your question about what this does to absorption.

DR. MAX: Is that a contraindication in the labeling at this point?

DR. SHOEMAKER: Yes, it is. It is in the labeling.

CHAIRMAN DOWNS: Yes, Dr. Foley.

DR. FOLEY: I wanted to make some comments related to, I think, the discussion that we were having earlier, that are sort of more broader principles, and I'm a guest at this meeting -- an FDA guest.

First of all, we have had a long experience of using intravenous Fentanyl for the treatment of chronic cancer pain, both in a hospital setting and a home setting, and we have not seen muscle rigidity at very large doses in which patients are rescuing themselves for breakthrough pain with 200 and 300 and 400 micrograms of Fentanyl.

So we have not seen it with a rapid IV bolus in a chronic, cancer pain population, and have a large

patient population. And after hearing this debate d makes me think we should report it.

Second of all, hearing this issue that w e have not seen or have not demonstrated tolerance t o respiratory depression with Fentanyl in a chroni c cancer population, and it would then assume tha t Fentanyl is so different than Morphine that all th e principles that we learned with Morphine and th e development of tolerance in the chronic cance r population which have been dem onstrated repeatedly in the literature, which recently the Institute o f Medicine said that every doctor should know.

And I'm concerned here, the FD A saying that this has not been demonstrated for Fentanyl, t o suggest that Fentanyl is different than Morphine and would need a whole other demonstration. So I thin k that -- I'm concerned about that concept that i t hasn't been proven and I'm com ing really, speaking as an advocate for the patient population.

The third issue is, do we know -- doe s anyone know -- in the population of patients wit h cancer, how many accidental overdoses by childre n occur at home situations? In the Memorial experience for the last 24 years, we have had two in a patien t population that has large doses of opioids in a home

setting in both a middle class , upper class, and poor inner-city population.

And we have two, well-documented instances in which both cases the children survived and which the drugs that they took were methadone because it looked like Tylenol, and MS Contin because it looked like a jellybean.

CHAIRMAN DOWNS: Other committee questions? Yes sir.

DR. ELLIS: John Ellis, Chicago. A couple of questions about chronic use. One I notice in the proposed label that cancer pain per se is not mentioned, but rather use for patients with chronic pain who are narcotic-tolerant. Perhaps that's something for us to talk about later.

It seemed that on a median or follow-up of 90 days of people in the chronic group that two-thirds didn't increase their dose, but I presume that means that one-third did increase their dose. I'm wondering if there was any substitution of the ATC narcotic in the patients who were in the chronic phases? That is, did they decrease their ATC use? Did patients find -- any switching from purely used as breakthrough to use as an ATC-type use?

DR. SHOEMAKER: There were no patients that

stopped their around-the-clock medications --

DR. ELLIS: Did they decrease?

DR. SHOEMAKER: Some patients did -- were able to decrease their medications because again, they felt since they were getting more effective control of their breakthrough pain that they didn't have to try to work as hard to prevent it, because when it came on they could get control. But I don't have the actual numbers. I know that occurred anecdotally, though.

CHAIRMAN DOWNS: Dr. Rothstein.

DR. ROTHSTEIN: In the deaths in the population that were treated, how did you rule out that these were not either respiratory-induced demises or hypoxemic cardiac deaths in the population?

DR. SHOEMAKER: I think as was pointed out by Dr. Kahn, many of these patients if they were admitted to the hospital, were not on OTFC at the time. And other than that, we took very careful histories and presented a narrative of each one of these patients. And in addition, those patients were included in the safety analysis that we described earlier with our four consulting clinicians.

CHAIRMAN DOWNS: Dr. Horlocker.

DR. HORLOCKER: Terese Horlocker, Mayo Clinic. I have a question for Dr. Kahn; I know she

raised this in her review in the literature we were given. Fentanyl and Morphine, when administered intravenously have about a 1:100 potency ratio and yet the data here suggests there's only a 1:10.

And I'm a little concerned about, that we might be underestimating that as we did with the Midazalom when that originally came out and compared it to Valium. And if we do underestimate, how potent the Oralet will be compared to Morphine -- we'll have some relative overdoses again. Could you comment on that?

DR. KAHN: I'm sorry, compared to IV Morphine, this 1:10?

DR. HORLOCKER: Yes, the --

DR. KAHN: Well, the relative potency estimate comes from the sponsor's data which is based on the study of patients who were in the immediate post-operative period and were given -- it was a double-blind study with either 2 milligrams/8 milligrams of Morphine or 200 or 800 micrograms of oral transmucosal Fentanyl.

I think that the problem with this use of the number, a 1:10 potency -- I think there is an intrinsic problem with that in that the two measurements that were used actually had entirely

different relative potencies. And if you look at the two endpoints that were used - - the total pain relief and the normalized weighted summed pain intensity difference -- the ranges were about 7 or 8:1 versus 10 to 14:1.

I don't think that it would be correct actually, in the labeling, to say that there is a 1:10 potency. I think that perhaps it would be more realistic to give that range as was found in the study, and also I think it would also be reasonable to get some more data. Because it's a very isolated patient population.

DR. SHOEMAKER: Could we have Dr. Portenoy comment on doing these types of potency assays and what kind of ranges are normally seen?

DR. PORTENOY: I think it's very important just to understand the limitations of the relative potency data that are out there. The relative potency data for Fentanyl that you cited comes from single dose, intravenous administration. And we know that there's a difference between single dose and repetitive dose and that relative potencies also change with the routes of administration.

And that's why three years ago I was a particularly strong advocate of going out there and

actually measuring it with this formulation, because you couldn't make the assumpti on that the data in the literature was generalizable to this formulation.

And so I think that the nice t hing that you have today is actual data from the double-blind , controlled trial that demonstrates what the relative potency is, and the limitations of that trial are wha t I mentioned before. It is single dose, it is a n opioid unexposed patients, and the patients have acut e post-operative pain.

And so just like we have learned to do i n the clinical setting with the current relative potenc y data as it is published on the equi-analgesic dos e table, we have to view these data as just guidelines for clinical practice; they're not etched in stone , they're not generalizable without clinical judgment. They're just guidelines; they're just data out there to help us know how to treat patients.

But without any question at all, you can't take the data in the literature that shows the I V relative potency single dose in the intra-operative o r post-operative setting and consider that to b e generalizable to OTFC.

CHAIRMAN DOWNS: Dr. Rohde.

DR. ROHDE: Chuck Rohde from J ohns Hopkins.

I have a comment and a question for both sponsor and FDA. I'm concerned about the titration data. As I understand it, individuals were followed through time, and I wonder why a correct analysis looking at individual profiles in doing a longitudinal analysis which is now available, was not done.

Because it seems to me that the truth is somewhere in between sponsor's data and the FDA analysis. The FDA analysis used episodes which are not independent, so it's not correct; the sponsor's analysis really doesn't take advantage of what the individual profiles might have been. And I really question whether those regression analyses mean anything at all.

So I'm just at a loss as to what the correct interpretation of that data might be without someone looking at it a little more carefully. The truth is somewhere in the middle, I think.

CHAIRMAN DOWNS: Would the sponsor like to respond to that?

DR. SHOEMAKER: Russ, could you help us with that one?

DR. PORTENOY: I could only respond by openly showing my ignorance. I'm not sure what truth you're talking about. The regression lines that I

showed were just an effort to relate baseline dose with successful dose after titration.

And I don't think that looking at the profiles necessarily would illuminate the issue of what the successful dose is in relation to the baseline dose which is critically important information for clinicians who have to select a dose to work.

I think looking at profile sounds very, very smart to me, and I know that the ability to look in a clever, statistical way at longitudinal data is evolving and now exists, and I think it sounds very smart. But I'm not sure what truth you're talking about, and it doesn't sound relevant to what I was saying.

DR. ROHDE: Well, the one regression plot there clearly has an influential point. The last point if you eliminated it would lower that R^2 considerably. And it's a very influential point, and you certainly picked that up.

DR. PATT: I don't want to gloss over the importance of that -- Richard Patt -- but to me in particular the conservative recommendations of starting at the lowest dose and titrating up, in part addressed this and also in part, addressed the other

issues that were raised -- the Fentanyl tolerance issue.

I think those are very conservative recommendations that will keep clinicians and patients out of trouble, because each patient really will serve as their own control.

CHAIRMAN DOWNS: Yes?

DR. MAX: Getting back to the relative potency issue, if you look at page 0041 of the handouts for Dr. Portenoy's talk, I want to emphasize, agree with the other panelists, that I'm very uncomfortable with the relative potency estimates for the main time of interest, which is the first 60 minutes.

The relative potency was constructed by taking, I believe, 360 minutes, and the most interesting time is what's going to happen -- the time of greatest danger is the first hour. And at that time this particular study with 30 patients or so in a group, had a very funny looking curve.

The 200 microgram Fentanyl group -- I think that's the one that shot up and was higher than any of the rest -- and I think if one took the first hour and tried to plot relative potency, it would be a very strange estimate.

I think the sponsor's conclusion on how to go about dosing it was very conservative, and I think their solutions though I am not very concerned about that, but I think if we want to instruct physicians about how to use it and how to compare it to IV Morphine, it may be very misleading to compare -- I think if you want to say anything about that at all you may want to get better studies for the first hour and do it.

DR. SHOEMAKER: I think there's two issues here. From an efficacy point of view again, we would not use relative potency to try to teach somebody how to dose; we would always recommend starting low. And from a safety point of view I think we have studies in progress -- to get at your issue more of peak effects -- and again, looking at OTFC compared to IV Morphine.

But I think as Dr. Patt pointed out, we wouldn't use relative potency to recommend how to dose this. Start with the lowest dose.

DR. RAGHAVAN: Derek Raghavan, Los Angeles. If you look at the demography of the patients that you've studied in each of the groups, the average weight is 70 or 71 kilograms with a standard error of the mean of about 2 kilograms. And given the fact that about half the patients are women I think you

could say that they're generously covered patients.

Now, for the indication that you're seeking, we're talking about -- to some extent -- terminally ill patients, many of whom will have cachexia. And so either the FDA or the sponsor, I'd like to ask the question, do you have any data for what must be a relatively small proportion of patients who are underweight and with cachexia, to suggest that there would be a difference in the disposition of the drug -- either the pharmacokinetics or the length of coverage -- before further pain dosing is required?

There would be some level of counter-intuitive thought -- fat stores versus dose per body weight.

DR. SHOEMAKER: I think first of all, we could maybe get you data on the range of weights, because there were clearly some patients at the very lower end. I think also, part of some of the variability in the pharmacokinetics and so on, might be taken care of by the titration process. Again, I mean, if you're starting low and you happen to be a thinner person you may end up on a lower dose, unless of course, your pain happens to be worse.

And so there's two different things going on, but again, the fact that you always start low and

titrate I think will account for some of that variability.

CHAIRMAN DOWNS: Dr. Rohde.

DR. ROHDE: Yes, the comment was made, we're not sure what longitudinal analysis would do. This is a perfect example of what it could do. Some of the explanatory variables could be weight, some could be height, some could be gender, and so forth. I mean, it would be possible to answer these questions with a sensible analysis. It is not terribly sophisticated given modern software.

DR. PATT: Yes, you know, again I need to keep coming back to -- Richard Patt -- to this information I think, would be very interesting and if this drug was ultimately proposed to be used in other settings, would be essential.

But as a clinician, the safety issues are really going to come down to careful individualization of care and this titration to effect is absolutely fundamental and what needs to be drilled into clinician's heads in terms of how to use a drug like this or other forms of opioids for treatment in breakthrough pain.

So while it's interesting and it is something that's worth looking at, I don't think that

it poses a safety issue in the cachexia versus the -- if these guidelines are followed of titration to effect on an individualized basis.

CHAIRMAN DOWNS: Yes, Dr. Wright.

DR. WRIGHT: I'd just like to comment that Dr. Rohde first instructed me in 1985 and he continues to instruct me; we'll want to talk with you about this analysis. Thank you.

CHAIRMAN DOWNS: I'd like to raise a point and I'm surprised that it hasn't been raised and perhaps it's my ignorance of the difference between the chronic pain patient, the patient with cancer with pain. And these terms have been used interchangeably throughout the morning. Most of the discussion of course, has centered about the patient with cancer who has chronic pain that is secondary to the cancer.

But it seems to me that the indications, the use and so on, are really for a much larger population; that's including patients who do not have cancer but who have cancer pain. And have I missed something in this or are they the same? And is the intent to be marketed for patients with chronic pain even though they don't have cancer?

DR. SHOEMAKER: I think we should first address the issue of cancer pain as a subset of

chronic pain, and perhaps let Dr. Portenoy discuss that. He's not only written extensively on cancer pain but also non-cancer pain -- excuse me, Dr. Farrar.

DR. FARRAR: John Farrar, I'm as I said, a neurologist at the University of Pennsylvania. I think it's important to understand that cancer pain is a large subset of patients which chronic pain. Chronic pain is clearly a very large and diverse group of patients. Cancer pain is a subset of that.

What makes cancer pain special is that -- a number of things. One is -- and I hate to admit this -- but one of the things is that we actually understand or we have a sense as physicians, as to what is underlying the process that is leading to the discomfort and the pain.

Differences in the categorization of pain was alluded to in one of the presentations by the FDA in terms of somatic and neuropathic pain. And I think another important issue to consider here is that in cancer-related pain we understand that, at least some component of their pain is related to somatic pain stimulation and some component is neuropathic.

In the chronic pain population as a whole -- if you look at chronic back or other types of pain --

it is likely that neuropathic pain, or nerve-related injury, plays a larger role.

Those two areas -- one, that in chronic cancer pain we understand or feel as physicians that we understand that the patient is in pain and are more comfortable with the fact that they are in pain, are more comfortable with the fact that we can give them opioids, it makes it a group of patients to target for opioid therapy.

With regards to the chronic pain population as a whole -- which is a much larger group -- we are less clear about the role of opioids in that population. In thinking about this particular drug it is important to remember that we are not trying to decide whether opioids are useful in the non-cancer population. And I think that the reason for leaving the indications the way they are is to specify the things that have to be specified with regards to any opioid use in these various populations.

The primary focus of the opioid use is in the relief of cancer pain which is an undermet population -- the need in that population is not well met. The potential use in the larger population of other types of chronic pain I think, is possible, but many, many physicians are uncomfortable with the use

of opioids in that population, and the way in which those patients should be selected and how they should be selected is an area that's quite controversial.

To get directly to your issue about whether these indications I think, are targeted at one group or the other, they are specifying that the population that it is to be used in is opioid-tolerant patients -- patients already on opioids.

That limits the group in which it will be used, predominantly -- predominantly -- to cancer-related pain or to perhaps, HIV-related pain, because that is the predominant group, in the United States anyway, that is currently on opioids.

So I think, in getting to your question, the reason that they're sometimes used interchangeably is because the restriction is on opioid-tolerant patients, and the predominant group that's opioid-tolerant and that needs this kind of pain medication, is the cancer pain population.

CHAIRMAN DOWNS: May I ask -- number one, I'm not sure that I completely believe the statement that most of the people who are chronically taking opioids have cancer. In our particular pain clinic there are a number of people going through detox for whom that would not be true, coming from our pain

clinic.

But if I understood you correctly, you basically said that this is being targeted mostly for people with cancer pain. But yet, people with chronic pain are a much larger group that don't have cancer. And yet, that's what I understood it was being targeted for. So still, you have not responded to my question to the point that I could understand it, anyway.

DR. PORTENOY: Maybe I could take a stab at it. I think the perspective here is that the role of opioid therapy in chronic, non-cancer-related pain is evolving, and it is a growing therapy.

And in fact, during the last year the Boards of Directors of both the American Pain Society and the American Academy of Pain Medicine have approved a consensus statement that recognizes for the first time in history, that chronic opioid therapy for non-cancer-related pain may be appropriate. And that's only happened in the last year.

This is in contrast to the cancer population where there has been recognition that opioids are the mainstay approach for a very long period of time.

So I think the point of view that John expressed was that patients who have chronic pain and

are now receiving long-term opioid therapy and have breakthrough pain, all of those patients might be considered for this drug.

And the indication doesn't exclude the larger population, but the focus on cancer pain just recognizes the reality that at the present time, the treatment of breakthrough pain in cancer patients using baseline opioid plus a supplemental opioid, is a mainstay, mainstream approach advocated by every organization around the globe and actively taught at multiple levels.

Whereas the treatment of chronic non-cancer-related pain using the same approach continues to be somewhat controversial, slowing evolving, and we wouldn't want an indication that excluded that but we want to recognize the reality and target it to the patients who can get the benefit most quickly. I think that's the bottom line.

MR. MAX: A couple of aspects of that. One is, with an indication for non-cancer pain, can the company promote it for that? On the other hand -- and I must say, I don't know whether with studies only in cancer pain, whether it's appropriate for them to claim an indication for a wider population where there haven't been say, safety studies, abuse studies, quite

as extensively.

On the other hand, the company has just said they are going to go after people who prescribe it for off-label uses. And as a clinician, if I wanted to give it to someone without cancer who had, say, a vertebral fracture -- terrible pain when they got up -- I certainly wouldn't want anyone hounding me to limit my prescribing of it.

So I think those are questions we need to address.

CHAIRMAN DOWNS: Dr. Callan, did you want to respond to that?

DR. CALLEN: Yes, thank you, Dr. Downs. I would just re-emphasize what I presented this morning of what a risk management program is. We are only going to focus our promotional efforts on the Hem/Oncs or the cancer pain specialists. These are the only clinicians that we will be approaching to give them information on this drug.

As a company we do not tolerate off-label use of our products. We are vigilant to try to educate clinicians who of course, have the right to prescribe any drug as they fit once it's approved and in the marketplace.

But we do not tolerate off-label use of our

products and particularly in something like this which is a new product. It's absolutely key that when it's introduced into the marketplace that it's prescribed properly, that it's used properly if it's to remain on the market without causing problems to patients.

It's similar to what we did when we introduced PCA in 1984. We knew that this was a technique for pain management for patients that was going to be extremely valuable. But we also knew that if there was any adverse incident associated with this therapy, that that would result in its elimination or physicians being reluctant to prescribe it and to use it on their patients.

And so that is also a program that we monitored very closely in the early days of its introduction and actually we continue to monitor it very closely today. So we're committed to what we presented in the risk management program that we will only be focusing our promotional activity -- our sales force will be directed to only interact with Hem/Oncologists and with cancer pain specialists for treating cancer patients. And it's only for those patients that are already on opioid therapy.

CHAIRMAN DOWNS: We'll go to Dr. McNicholas, then Dr. Strain, then Dr. Lowenstein, and then we'll

cut it off at that. Dr. McNicholas.

DR. McNICHOLAS: I think I'm more confused than I was before and perhaps this needs to wait until after lunch because the package insert says that it's for chronic pain patients who are opioid-tolerate, and yet we're hearing that it's actually going to be marketed only to cancer patients and we have no data on patients who are not cancer pain patients.

And so I'm frankly not sure what the indication that they're actually going for is. I'm not sure how this indication should be phrased; whether it is for chronic pain patients or for cancer pain patients.

CHAIRMAN DOWNS: I'm going to assume that was a statement and not a question --

DR. McNICHOLAS: You're right.

CHAIRMAN DOWNS: -- and go to Dr. Strain.

DR. STRAIN: I was going to essentially make the same point, that --

CHAIRMAN DOWNS: Good, then we can move on to Dr. Lowenstein.

DR. LOWENSTEIN: I was going to put this in the form of a question. Isn't it inevitable that HIV patients will be -- that this will be indicated in HIV patients who are a very large group now who are

requiring opioid therapy?

CHAIRMAN DOWNS: I'd like to hear the sponsor's response to that before we adjourn for lunch. Dr. Portenoy.

DR. PORTENOY: This is one of the reasons why I think it's important to not be too restrictive in the indication, irrespective of how it's ultimately, initially promoted.

The Agency for Health Care Policy and Research Guidelines on Cancer Pain specifically stipulate that HIV-related pain ought to be treated like cancer pain. And there are now a small group of studies that are coming out to show that HIV-related pain is very similar to cancer pain in its prevalence, in its phenomenology, and the main difference relates to under-treatment. It's much more under-treated than is cancer pain.

There is no reason to think that the availability of this drug might not be useful in some patients with HIV-related pain. So we would want the indication not to be restrictive, although again, for the reasons that Clair Callan mentioned. The initial promotion would be to those people who are most experienced in using opioid therapy, and those are cancer pain specialists and oncologists.

CHAIRMAN DOWNS: I guess I have to make an exception. Dr. Wright.

DR. WRIGHT: I'll try to be brief. In the past we have not, as a Division, differentiated between cancer pain and other forms of severe, chronic pain requiring opioid therapy, except as pertains to occasional matters of safety as have already been brought up and discussed by the committee.

Usually in testing we require that the drug be tested in a suitable, chronic pain model, and that is usually cancer pain for a chronic opioid, although not exclusively. We had not entertained the notion of marketing an oncology-only analgesic, simply desiring not to make other classes of patients therapeutic orphans.

There is a concern, and a legitimate one, that chronic pain is sometimes in the mind of the prescriber, and as a result, we have seen a number of misadventures involving strong, potent opioids that have been inappropriately prescribed for lesser indications and in patients where wisdom of strong, opioid therapy has not been demonstrated.

So bottom line, we don't think that there is a specific cancer pain indication related to opioid narcotics -- or haven't yet thought that.

CHAIRMAN DOWNS: We'll break for lunch . We'll be back here and re-adjourn at 1:30.

(Whereupon, a brief luncheon recess wa s taken at 12:36 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

1:33 p.m.

CHAIRMAN DOWNS: I'd like to call the meeting to order once again. According to the agenda we now have time for further committee discussion. There are a number of people who still had issues to discuss when we took the break for lunch so we'll try and entertain those first. Yes?

And again, I'd like to ask everyone to speak into the microphone and identify yourself before you speak.

DR. de WIT: I'm Harriet de Wit from the University of Chicago and my question is one from the drug abuse perspective. I was wondering about the post-marketing surveillance plans, and also whether we have any information available from the prescription use of the other form of transmucosal Fentanyl; whether there have been any reports of abuse, what kind of information, what their level of prescription use has been.

So I think it's important to get both the numerator and the denominator to look at the reports of adverse events or misuse or diversion in the context of the number of units that have been prescribed. And I'm interested in what kind of

mechanisms might be put into place for monitoring this new product.

DR. KLEIN: Can I just respond? The numbers for Oralet are very low. For '95, something like 11,000 prescriptions and for '96, 6000 that's going to IMS.

DR.de WIT: And the reports of misuse, diversion, adverse effects?

DR. KLEIN: Oh, I don't have any reports for Oralet.

DR. WRIGHT: Oralet, zero.

CHAIRMAN DOWNS: Dr. Shoemaker?

DR. SHOEMAKER: No, that's our experience too. I think about 35,000 units of Oralet have been distributed and we're not aware of any reports of abuse and misuse with Oralet.

DR. McNICHOLAS: First of all, I would like to point out that Oralet has a very limited distribution; it's not widely available. Which brings me to one of my major points -- and I'm glad you brought this up, Harriet -- and that is, I have some questions on the risk management plan.

First of all, let me state that I don't think that the cancer patients -- I don't think chronic pain patients in general -- are going to be

the ones abusing this drug. What I am concerned about and as a substance abuse person I am concerned about is, if this drug is available in the corner drugstore are we going to have diversion?

And there are two issues that I see here. One is, we have been presented with no data on the reinforcing properties of this dosage form. We're looking at the highest end of the dose that they're asking for -- 1600 micrograms of Fentanyl -- which is a whopping dose of an opioid and bound to have some reinforcing properties, but we're not getting any data on that.

The other thing is, one of the major things -- proposals in their risk management is that they're saying that by limiting the number of wholesalers they're going to prevent diversion. And I was wondering if we could get clarification on: a) how does limiting wholesalers prevent it from becoming available in the corner drugstore; do they anticipate it becoming available in the corner drugstore?

And my concern from a substance abuse point is that it's going to become available via doctors who write prescriptions for money -- script docs, etc., and other unethical practitioners -- not that it's going to be necessarily -- well, you also have the

issue of some teenagers stealing grandpa's medication.

But that's minor compared to some of the damage that could be done if you get this available by people writing prescription mills.

DR. SHOEMAKER: That's an issue that we've looked at, and I would like to ask Dr. George Bigelow to address those issues.

DR. BIGELOW: I'm Dr. George Bigelow, professor of behavioral biology at Johns Hopkins University School of Medicine, where I specialize in clinical studies on drugs of abuse and of drug abuse and its treatment.

I've served as consultant to Anesta Corporation in evaluating abuse liability aspects of the OTFC product, and I've helped with writing the Abuse Liability Section of the NDA application. I've not worked directly with the OTFC product but we felt that there was in fact, considerable data available about the clinical pharmacology of Fentanyl and about the pharmacokinetics and pharmacodynamics of the OTFC product that allows us to reach reasonably good predictive conclusions about the relative abuse liability of the OTFC product.

Abuse liability is determined on a couple of factors: the pharmacology and the availability. I

think Dr. McNicholas has talked largely about the availability aspect.

It's important to recognize that this product is going to be of very limited availability. On this schematic diagram of a continuum of availability relative to other drugs of abuse, it's important to understand that all these opioid products are down toward the low availability end. This product will only be introduced into homes where other chronic opioids are being used, so there is very little population exposure to the compound.

Now, there are a number of populations that one might consider as being at risk when a new product is introduced, and these range from the patient populations themselves to family and friends, other household members, pharmacists and other individuals in the distribution network who may be handling and distributing unopened packages of medication, as well as physicians and other health care providers who may have access to the product in either sealed or unsealed form -- as well as drug abusers themselves.

Now, our characterization and understanding of the pharmacology and availability of this compound lead us to believe there will not be significant risk of abuse of the OTFC product relative to the other

opioids that are available in these contexts, when one considers these different populations.

There are a variety of factors that mitigate against the risk of abuse, and we thought that these factors are relevant to making us feel relatively confident that with all of these patients who are in the controlled subject populations, the risks will be relatively low.

We're not -- understand, we're not saying there's no risk of abuse. We're saying that this is appropriately categorized as a schedule II narcotic with all the restrictions appropriate to that category. But within that context, relative to the other opioids, there are many features of this product that will make the abuse relatively lower.

The schedule II restrictions themselves are going to minimize the availability of the compound, it will increase the protectability of any abuse and diversion. The limited availability is simply going to reduce the chance of individuals who have access to it.

The slow onset pharmacokinetics and pharmacodynamics will make it relatively unattractive to serious drug abusers who will only use drugs for rapid onset effects. So relative to intravenous

compounds, the OTFC product's slower pharmacokinetics and pharmacodynamics will make it relatively less appealing.

It's in a form that's relatively not very easily divertable to injectable use. So again, this is a dimension that will make it relatively less appealing to serious drug abusers. The visibility of use by the transmucosal group is something that -- of users said this is an illegal behavior and usually will try to avoid. And that visibility will increase the likelihood of detection of any diversion.

The bulkiness of the product and the fact that the unit packaging allows very careful auditing of the number of individual units makes the attractiveness of theft less so than with highly concentrated products such as tablets or solution. And the bulkiness also increases the detectability -- the bulkiness and audit ability also increases the detectability of any theft from pharmacy situations.

So I think that it would be much more difficult for undetected theft of this product to occur in the community pharmacy than would be the case with tablets or oral medications which are dispensed in bottles and patients don't really count the number that they receive.

Finally, I think the company's professional education program will emphasize the importance of using this product appropriately, prescribing it only into households with individuals who have concurrent opioid use. And finally, the relative cost of the product will make it relatively unattractive for diversion and abuse in any context in which the proposed abuser has to pay for the product.

So concern about unscrupulous pharmacists, unscrupulous script doctors supporting abuse in the context that patients would have to cash in the prescriptions, pay for the prescriptions, the relative cost of Fentanyl by the OTFC group is substantially higher than with other dosage forms that are available. And these are figures based on the 100 microgram Fentanyl equivalents.

I'll stop there. If there are more specific questions I'll be happy to answer them.

CHAIRMAN DOWNS: Please continue, then.

DR. McNICHOLAS: George, you know as well as I do that, first of all, drug abusers will use anything. To say that this is not convertible to an injectable use is I think -- we would like to look at it that way but if you've got 1600 mics of Fentanyl in 5 cc's of sugar syrup, sugar syrup never stopped them

from injecting. They inject talc, they're going to inject sugar syrup if they want to.

But I'll tell you, I don't think that it's going to be your established opioid addict that's going to be most at risk for abuse here. I think it's going to be your college-age kind, your young adult who wants a weekend party drug. And I'll tell you, my nightmare of this is having 20 kids out there having a party all of them, so that they can have a lollipop party. And 18 of them don't wake up the next morning.

And my issue here is not that people are not going to do this. My issue is, what are the steps being taken? I've heard limited availability, limited availability, but I haven't heard exactly how that availability is going to be limited.

And my issue here is for the first time in my professional career, we are finally getting to something approaching rationality in the treatment of pain and we are stopping this demonization of the appropriate use of opioids. And if something like this happens and it gets on Good Morning America and Nightline and everything else, I don't want us going back to where we were 20 years ago when you're treating cancer pain with aspirin.

And I really see a danger that if something

like this gets out we're going to have a horror story.

CHAIRMAN DOWNS: Let's proceed. Let the sponsor respond and then --

DR. BIGELOW: Just a bit more. Let me make clear that I -- we don't suggest at all that this is a product without abuse liability. This is a schedule II narcotic and it needs to be very closely regulated. This product certainly has some abuse liability.

We thought that the schedule II restrictions and risk management plan of the sponsor were adequate to minimize the risk associated with a known drug of abuse. There's no question that Fentanyl is a known drug of abuse.

There are a couple of factors in addition to the known pharmacology of Fentanyl that do make everyone worry that this is a product that may receive some attention from potential abusers. The onset will be faster than with oral medications, but again, in the typical situation, individuals who have access to this product will have access to other opioids, have access to less expensive opioids, and will have access to opioids that could equally well be used by equally rapid routes of transmucosal administration, even though the dosage forms may not be designed for that use.

There are a couple of speculative concerns about which we really have no data, about we thought. And these are the two listed here. That the route of administration may in some way allow those individuals such as you were describing -- young individuals who were interesting in experimenting with drug effects, who see injection as a behavioral hurdle that they're not willing to cross -- may be more willing to take this dosage form.

There's no reason to think that this dosage form is any more attractive in that right than are oral dosage forms, which should also be equally available. The other speculative concern is, perhaps there's a perception of individual dosage control or titration being easier with this product. An individual may think, oh I'll just suck a little bit and I'll be able to stop; whereas with oral dosage forms -- in other dosage forms there may be more of a bolus ingestion congestion consideration.

Both of these are speculative. We recognize that these are risks, and I think the company sponsors will have to address the risk management plan. We've just sort of thought about these issues and we've thought the risk management plan is sufficient to minimize the possibility that these speculative risks

might come to fruition.

DR. HEDEN: Dr. Downs, if I may address the issue with what added safety the wholesaler restriction provides? As you know, there are a number of elements of the risk management plan, one of which is to restrict Abbott's direct sales to drug wholesalers.

Certainly, all opioids that are in this population are available at retail pharmacies and it is our intent that *Actiq*™ will be available at retail pharmacies but it will not be sold directly by Abbott Laboratories to a retail pharmacy.

What this does is, it adds another layer of protection to the program because the DEA-222 forms, etc., the schedule II requirements, are on each level of distribution. So by adding the drug wholesaler in there there's another level of accountability, another level of inventory control, another level of monitoring that will go on in this situation.

Each drug wholesaler has localized warehouses and distributions with vaults. This will minimize the amount of inventory that has to be held in an individual pharmacy which we think will reduce the amount of abuse potential.

In addition, this will allow us to monitor

at a local level, the script volume and the retail pharmacy volumes that are being ordered on a routine basis. This is the type of information that we will monitor continuously in order to identify areas where potential abuse might be occurring. And as Clair indicated earlier, respond immediately with a SWAT team to go in and find out, in conjunction with DEA officials, to find out if there is any abuse occurring.

But that's one extra level, an additional level, that we've added into this process. We could sell directly to the retail pharmacist, but this adds another level of protection.

CHAIRMAN DOWNS: Dr. Strain and then Dr. Watcha.

DR. STRAIN: Thank you. Dr. Strain from Johns Hopkins. Let me actually try to respond, George, in a way to maybe help you, although you probably don't want to hear this.

I think the dilemma in answering Laura's question that we don't have any data to make a determination of this -- and I think that's what's somewhat problematic here -- is that there's surprising that there's no study that tells us the relative abuse potential in, say, opioid-dependent

patients, of the transmucosal Fentanyl compared to an IV administration of some other drug of abuse.

And similarly, a study in a non-opioid -dependent population comparing the transmucosal at different dosages to some other known reference compound. And that might I think, give us some -- allay some of our concerns -- or alert us.

While you're getting to the microphone -- well, I have a couple other comments on the abuse potential related to that, but do you want to respond to that?

DR. BIGELOW: George Bigelow again. Let me first address the issue of why there were not abuse liability studies done. As you know, I love doing abuse liability studies -- it's the type of work I do -- and we discussed this quite a lot as to whether there was any value to be gained from conducting that type of study, and concluded that there really wasn't.

We're acknowledging the schedule II appropriateness of this medication; we're recognizing that this is a drug of abuse that should receive that level of scheduling and control. We didn't feel there was anything necessary that we needed to know about the abuse liability of Fentanyl in this particular dosage form, given that the abuse liability of the

medication itself is so well documented.

We're estimating that the 400 to 800 microgram dose will be a dose that experienced opioid abusers will produce some euphoric effects, and that's based upon all of the pharmacokinetic data that are available, both from the company's work as well as the prior clinical pharmacology work with normals and with abusers, with Fentanyl.

DR. STRAIN: Well, let me go on to another point then, that maybe addresses this again in a different way which is, the whole question -- you know, in a way the sponsor has presented things wanting it both ways. They say that this product has a rapid onset of action as an analgesic, but then has a slow onset of action which decreases its abuse potential.

And so I think that's the sort of distinction that might be useful to tease apart in a study. Let me make a couple of other points on the abuse potential and then I'll sit back.

I think that this may have some attraction in other ways to the IV drug abuse population. For example, since it is not an intravenous route but has a relatively fast onset of action, it could be attractive because it decreases IV risk of hepatitis,

HIV, while giving a rapid onset, short acting drug effect. So it may actually have some attraction in that respect.

And another reason it may be attractive to the drug abuse population is because it will be a relatively unadulterated product if it gets on the street. It isn't like something somebody's going to be able to cut this product and sell it as being relatively pure.

They could sell the product as the intact product, and if somebody smashes it into pieces or something, that's going to be self evident. So you'll know if you're buying this product on this street that you're getting the product in its entirely -- which may have some attraction as well.

And finally, I would just comment that it's interesting in reading through the materials, that when this did come up as Oralet several years ago now, two consultants discussed that the advantage to Oralet was that -- with regard to risk potential -- abuse risk potential -- was that it was going to be in very controlled environments and situations, and that's why the committee at that time should feel comfortable approving it.

So at that point that was, it seems,

acknowledged indirectly as an important factor; that it would be under controlled situations. And now we've lost that. I'll stop there. Thanks.

DR. BIGELOW: George Bigelow. I've lost track of all those questions but I remember some of them. On the speed of onset question, I think we've been very explicitly acknowledging that this compound falls intermediate to intravenous administration and oral administration in terms of its speed of onset. We've also made that point with respect to the availability.

Fentanyl has traditionally been abused by the intravenous or injection route, so relative to the history of Fentanyl abuse, this is a product that has slower onset, and consequently we believe, lower abuse liability. We've acknowledged that it will have somewhat more rapid onset than oral dosage forms, and so I think there's been no inconsistency in the way we're characterized the drug, in this respect.

If you can prompt me some more on some of these other issues I'll try to respond to those also.

DR. STRAIN: That it would be an attractive product to the IV drug abuse population for example. It's pure, it's intact, decreases IV drug abuse.

DR. BIGELOW: I simply don't see that as

being true. Intravenous drug abusers are by and large, going to be seeking intravenous, rapid onset drugs of abuse. Or, if they're choosing to administer a drug for withdrawal suppression, they'll look for a drug with a long duration of action, rather than a short duration of action, such as Fentanyl will have.

So I think, within the intravenous drug abuser population I see this product as being least appealing. It's a bulky, expensive product that requires a good bit of effort to convert to an injectable form, which is the form they would desire. The detectability and cost are too great to make this competitive with heroin.

DR. CICERO: This is Ted Cicero. I'm a consultant also for Anesta from Washington University School of Medicine. I think the point we're missing here is, this is a schedule II. No one's disputing it's a schedule II. There's going to be some abuse potential. I would suggest that Laura, Eric -- we're all speculating about what's going to occur and you're right -- there are no data.

The only previous experience with a compound like this was at a hospital, a controlled setting, and I think that's the underlying concern with the group here, and I suspect that's why there's been zero cases

of abuse with that. And it's all that -- it's predictable because the exposure wasn't so great.

So a couple of issues you have to ask yourself. How much exposure is there going to be with this compound? Is it really going to be, as Laura suggests, widely distributed by retail pharmacies and is it going to enjoy popularity beyond what the group that it's intended for? I think that part of the company tried to confine itself to a very specific population -- indeed, to omit the amount of exposure.

And looking at chronic pain patients, particularly those with recurring bouts of pain or rebound pain, I think we're going to attempt to limit the exposure to 800,000 to a million potential customers or households, if you will, the first couple of years.

But George is speculating, I'm speculating -- let's just be candid -- we're all speculating. We don't have any data. I think this is why the company -- and I think they need to perhaps go over that again -- has proposed a very proactive surveillance effort -- to get out there are find out whether abuse is occurring.

I think we think it's highly unlikely that it will occur. There's lot of arguments for it, but

Laura's got a good point. I don't know. We had a situation 10, 15 years ago where a cough syrup attracted a lot of popularity with some kids. It's possible.

I think all you can do is try to detect these sorts of things as they occur, gather some data on the move, because this is a new formulation, we have no data on it, and I think the company's surveillance efforts will pick up that data. Because right now I think we can speculate the rest of the afternoon in terms of, is it likely or isn't it likely? And the answer is, I don't think any of us have any data at this point to have done it.

The abuse liability assessment right now -- it's an interesting question. When I first looked at this packet six months or so ago, that was a question I had as well. But to get to George's point, all right, so it's a schedule II. I'm sure you would confirm this is a schedule II. Well that's what, in fact, he's arguing.

So the essential point boils down to, what is it about this candy -- if that's what the issue is -- that is going to make this inherently more attractive to the drug abusing population?

And for the life of me, I can't think of a

reason why a lollipop piece of candy would be more attractive to IV drug abusers or to recreational user on the street -- I can't for the life of me rationalize it. That I would argue that ranking-wise, this compound would have less abuse than most other schedule II compounds.

But I'm speculating. I think the proof will be in what we can pick up.

DR. STRAIN: You can never argue against wanting more data, and I guess I'm just asking -- and I wouldn't say, well you don't need post-marketing surveillance data. I'm just wishing that there had been more pre-marketing data --

DR. CICERO: I understand your point, but again --

DR. STRAIN: -- there's no data on abuse liability regarding this formulation of Fentanyl. Nothing.

DR. CICERO: It's a given, Eric. It's a given.

CHAIRMAN DOWNS: We're beginning to get a little bit out of hand here. I clearly see all the hands down there and we'll take them, but Dr. Callan would like to respond and then Dr. Foley and then Dr. McNicholas.

DR. CALLAN: Just to try to allay some of the concerns about how we're going to collect data of possible drug abuse or misuse or diversion, etc. I mentioned this morning that we were going to be doing an ongoing monitoring of different surveillance programs that are out there, and the two principle ones that we're going to be doing are the NDTI and the National Prescription Audit, both of which will give us information, as I said, on a quarterly basis as to who's prescribing the drug for what indication.

And you can check very easily there and see whether the oncologists are prescribing *Actiq*™ or whether dermatologists -- terrible thought -- would be prescribing *Actiq*™. So that will give us an indication of whether or not it's being used appropriately.

Also, in addition to this long list, we are working with the Drug Abuse Warning Network, or DAWN, as to ways to try and collect information in this area that will be of benefit to us all.

And then there are several different surveys that we are considering doing with different groups, particularly with the school nurse, drug abuse coordinator, and other areas where we may be able to pick up some of this information on an ongoing basis.

And be able to report it back to the FDA at regularly scheduled intervals.

So I hope this addresses some of your concerns; that we are going to make an effort to try to continue to get this information.

CHAIRMAN DOWNS: I believe Dr. Foley was next.

DR. FOLEY: I think that these are very important issues that are being raised about this whole question of the drug abuse issues. But I think I'm going to just put it in a little bit of a broader perspective.

Every day there are 1400 cancer patients who die. The data that we have as best we can know, is about 50 percent to 60 percent are dying either in a hospital setting or in some kind of a hospice-type program, or some other institution. So that -- and upwards of about 70 percent of those patients have significant pain.

In any one day there are about 100 patients around the country who are dying on IV narcotics at home, with PCA pumps. And so if we're going to put this in the perspective of that population, of those patients in which there's the IV access that you'd be worried about and the abuse liability is out there in

this population.

And both the hospice data and the data that we have coming out of DAWN and everything else that exists, is not demonstrating an enormous diversion of this drug into some other populations or kids coming to the house and having a party with their mother or father's PCA pump.

And I think we should -- I really respect our concerns about it. I think we can worry about the issues of abuse liability. But all the data that was done by the drug addiction centers over the years, has not predicted what happened in the cancer population when we put drugs into that population.

And so that this information is important; it's something we need to worry about. We have to be absolutely careful about it. But I think that -- I have a concern that this is sort of -- that his discussion is moving away from the needs that we have of a patient population for getting adequate pain management; the needs of having a drug by a unique route for patients who can't swallow; and I think putting it in that framework. And I think the FDA needs to understand that someone should collect this data on every opioid that's out there so we can begin to make these decisions.

CHAIRMAN DOWNS: I believe Dr. Watcha had a question long before anyone else did.

DR. WATCHA: In connection with the statements Medwatch at Dallas. In connection with your previous statement, request from the FDA if they have any information about misuse of MS Contin for either intravenous route or otherwise.

DR. WRIGHT: I must confess to be at a loss -- which is a rare event -- but we do know that there are cases involving abuse of MS Contin. I do not know if they are parenteral or if they are oral. And I have no knowledge of the relative rate with respect to other products.

I am hearing something that I would like the Chair to -- or the members of the committee to articulate for me though, because for many years we have had -- not a policy, but it's never occurred to us that if we were going to put something in schedule II that we needed to do abuse liability testing on it. Because what else were we going to do?

What I'm hearing is that it may be time to view abuse liability and addiction as one of the risks of the drug, and that risk should be delineated so that we can factor it into the risk benefit analysis that we make in terms of the relative merits of an

application.

But if you could articulate that, we really need to hear that. We really need to understand exactly what knowing the relative abuse liability of this versus intravenous Fentanyl, would help us decide.

CHAIRMAN DOWNS: Dr. McNicholas.

DR. McNICHOLAS: If I can try and take a stab at that for you, Curtis. My concern is -- and I think there's no question from anybody on this table that IV Fentanyl can be abused; that's a given.

The drug abuse scene on the street is changing, and it's changing in way that 10, 15 years ago, and particularly prior to HIV, we never could have predicted. The patients that I am seeing coming in for opiate-dependence treatment under the age of 30, have by and large, either, a) never used a needle, or b) decided to seek treatment shortly after starting using a needle because they started snorting.

And 10, 15 years ago you never saw snorters of heroin or any other opiate, coming in for treatment because it just wasn't a phenomenon. Drug abusers on the street today are actively seeking alternate means of drug administration so that they don't have to inject -- which is exactly what Eric was saying. They

know the risks of injecting -- or at least some of them do -- and they would prefer not to. But a lot of them move to it eventually anyway.

My concern with the abuse liability of this product is, we have no data in a transmucosal form, on its reinforcing effect. Given the fact that it is Fentanyl, I am quite sure that at least at the higher dose levels, and probably 400 and above, as George says, is probably there.

What is its abuse liability? Are we looking at something that we need to look at a control on? And I don't mean to discount Dr. Foley's point because her point is absolutely right. We have been denying patients adequate analgesia in order to protect the population from abuse. And you have to be able to balance that.

But is there some way that we can balance it by limiting distribution rather than limiting it to wholesalers by limiting it to chronic pain clinics, to hospice situations, either at home or a live-in hospice, or home care health professionals or something that would not put it in the CVS on every other corner?

And that's where I think abuse liability would help us make a reasonable decision. If the

liability is low enough by the transmucosal route that you're not going to get a particular diversion then fine; put it in the CVS on every other corner. If it is then maybe we need some unique and some creative thinking on how to get this to the patients who need it without exposing a population that is thrill seeking and likely to get into trouble with it.

CHAIRMAN DOWNS: You're going to respond to her?

DR. CICERO: Yes. Again, I think I go back to Curt's point; we agree on this one entirely. If you went and did the abuse liability assessment testing now in the traditional paradigms that we have, you're going to come back and say this compound has abuse potential.

I am very comfortable that that's exactly what you'd find. I'd be astounded if you found anything else than that. Therefore, the company recommends a schedule II, which is certainly consistent with all other schedule II drugs.

Now, are you going to suggest that if it's worse than some other schedule II drug it be made a schedule I? See, I don't know where you go once you've determined that you've got abuse potential, except I think you're raising a different issue with

respect to -- it's a schedule II; the abuse liability assessment will tell you it's a schedule II.

You may well then, want to look at contemplative ways in which the access of this drug is restricted; and that's your point.

DR. McNICHOLAS: That's what I'm talking about. And that was what we did with the Oralet. That was restricted to anesthesiologists and surgical centers.

DR. CICERO: I understand that. I just wanted to clarify where we're coming from, because we're not divergent; we all agree.

DR. McNICHOLAS: No, not making it schedule I and not making it inaccessible to the patients who need it, but coming up with some creative ways to control the access.

DR. CICERO: I just want to make clear -- we're not talking about abuse liability in that case because I think the abuse potential of this drug will be equivalent to others in a schedule II. The issue you're raising is a secondary but equally important one: how do you limit its access to potentially vulnerable populations? I believe that's your point.

DR. CLEARY: Jim Cleary from the University of Wisconsin. I'm Director of Palliative Medicine at

the UWCC and a Hospice Medical Director, and I'm particularly concerned to hear this limitation.

The practice of oncology has changed dramatically in the last 20 years. Dr. Raghavan can talk to that. Twenty years ago the UW had two wards full of cancer patients receiving their treatment. We're now struggling to justify having six beds in the University of Wisconsin. Cancer treatment is outpatient treatment; it has to occur in the outpatient setting.

Most cancer pain management, although it's not done well by oncologists, is done by hematological oncologists and oncologists, not by separate pain clinics. It's done by the cancer treaters. We cannot limit this product purely because of its formulation. It is Fentanyl. There is something like 7.2 grams at least, of Fentanyl in a Fentanyl patch.

There are people who cut up the Fentanyl patch and misuse it -- 7.2 grams -- and yet we are talking about limiting the supply of this drug to cancer patients who need it because of maybe someone getting hold of a 1600 microgram patch -- or sorry, 1600 microgram lozenge. We need this product, we need it available to cancer patients in the home.

CHAIRMAN DOWNS: Does the sponsor still wish

to respond to --

DR. SHOEMAKER: I think there was a question raised about potential abuse of other opioids, and I was wondering if Dave Joranson could comment on that?

DR. JORANSON: Thank you, Mr. Chairman. My name is David Joranson. I am with the Pain and Policy Studies Group at the University of Wisconsin Comprehensive Cancer Center. I'm actually a former drug regulator now working on pain policy in the analgesic field, particularly in cancer, and I'd like to respond quickly to two points.

One of the members of the committee was asking I think, the question, to what extent is there some data on the misuse of other opioids such as Morphine? We have a Robert Wood Johnson Foundation Grant to look in part, at that subject.

And on a preliminary basis we have received information from NAIDA, or is it SAMSA, on the Drug Abuse Warning Network, on the number of mentions of Morphine in the DAWN system. This is emergency room mentions where this particular drug, Morphine, turns up in a patient as part of the reason for the admission to the emergency room.

And over the past 15 years the percentage of Morphine mentions of total episodes of admissions to

emergency rooms in this reporting system runs at about .0015 percent of all the episodes. Typically, the category that includes Morphine is connected or included, in a category called Heroin/Morphine. And so we've never been able to tell how much of that was Morphine and how much of that was Heroin.

And so the data run that we've just gotten has helped us answer that question by telling us that the Morphine component of the Heroin/Morphine category is extraordinarily small. And, I should point out, has appeared to remain quite stable over the period of time of the last ten years when the medical consumption of Morphine in the United States for medical purposes has increased by many factors.

The other point I'd like to make is, as a former drug abuse person and controlled substances regulator in Wisconsin, I'm also concerned about the issue of potential abuse and diversion of any new opioid product -- not only from the point of view of preventing public health damage, but also promoting the public health value of these important drugs and to achieve some kind of a balance here.

When you think about diversion I think there's three ways diversion basically occur: one is through pharmacy thefts, the other is through script

doctors, and the third one is through forgeries. I don't know that we're going to be able to do much about pharmacy theft. This is a subject of criminal intent and is basically a law enforcement response.

But DEA can't tell us how much of any controlled substance is lost or stolen from pharmacies. All we have to do is ask them and it's on the DEA-106 Form which pharmacists must fill out every time there's a loss. And so it's possible for us to ask the question, how much of any of the opioid analgesics are actually being diverted because of pharmacy thefts anywhere in the country?

So I'm going to put that aside. The other two are equally difficult to deal with but maybe more responsive to education and some of the methods that have been proposed by the sponsor.

If a drug gets to the point of being popular and having a street reputation and becomes in demand -- I mean, I don't think it's going to happen with this product but if it did -- I think that the two ways that you're going to be able -- that a person, an abuser would get the drug -- would be from a pharmacy.

And the way to get the drug from the pharmacy is through a prescription. And that you either forge the prescription or you get a doctor who

doesn't care what you use it for, to write it for you.

And I think it's important to note that in this case, the sponsor's proposal for working with and educating pharmacists, coupled with the labeling and contraindications piece for this product, is such that the pharmacist is going to serve as even an added control, other than the fact that it's going to be a schedule II drug, written prescriptions, no refills, and only for a legitimate, medical purpose.

In addition, the pharmacist is going to be in a position to see something pop up on the screen, to have that pharmacist ask the person who has the prescription for ***Actiq***™, what other medications are you taking? And if they can verify that they're taking another opioid medication, that might be sufficient to allow the dispensing.

But if in fact, that looks like a very weak situation and the call goes to the physician to verify, as pharmacists are counseled to do all the time, I think we can have an extra strong check and balance here that is likely to occur to prevent this type of diversion.

Not to say that people aren't going to become more creative, but I think that in the look that I've had at the sponsor's plans, I think that

they exceed the intentions of most other sponsors in the past. And I think that this discussion has gotten increasingly sophisticated over the last 20 years, and I really wish that some of the products that have been marketed in the last 20 years had been subjected to this degree of scrutiny and discussion.

Because it hasn't, I think some of the products that are on the market today have gotten out of control to some degree and have resulted in a higher profile of abuse than was necessary, and a much greater investment on the part of the authorities -- regulatory and law enforcement -- as well as the companies, in order to deal with these problems.

I think what you're seeing here is a thought-out, thorough, and deliberate approach to try to prevent that problem before it starts.

CHAIRMAN DOWNS: Does the sponsor still wish to respond further?

DR. JORANSON: No, Dr. Downs.

CHAIRMAN DOWNS: Okay. I believe Dr. Ellis was next, although I have to admit it's been so long my memory is getting a little vague. I'm sorry, Dr. Ellis.

DR. ELLIS: John Ellis, Chicago. More a comment for the sponsor than a question, but I look at

the FDA presentation and see that there's a quota 30 times as large as when I finished my residency, for producing Fentanyl. When you look at people who have a choice of narcotics to abuse -- that is, anesthesiologists in treatment -- Morphine is rarely used.

So I do wonder about the decision not to do reinforcing studies on Fentanyl versus Morphine, which is the other narcotic we're talking about. And with that, sort of echo the question that Dr. Wright had: do there need to be separate considerations of abuse liability of class II compounds.

CHAIRMAN DOWNS: That was a statement rather than a question, correct?

DR. ELLIS: That was a statement.

CHAIRMAN DOWNS: Let me move to Dr. Temple because I know you had your hand up a long time ago, and then a sponsor wishes to respond. I'm sorry, Dr. Klein. Excuse me.

DR. KLEIN: We do have some numbers for the different morphine products, but I was just looking at them last night and they're not fully analyzed. But there are a certain number of reports of, primarily misuse of the product and possibly some abuse as well. But frankly, it's hard to tease out, in the case of

Morphine, when there's reports of death involving Morphine; you know, it could also be Heroin where Morphine was analyzed.

So you know, I'd rather not get into any more specifics about those numbers until we look at them in greater depth.

CHAIRMAN DOWNS: Sorry, Dr. Klein. Dr. Wright?

DR. WRIGHT: Yes. I think I -- let me take another crack at Dr. McNicholas' question and statement and observation, because I think they're all three and they're all good.

I think it's necessary to fully discuss what we're trying to prevent. One of the things we're trying to prevent is the introduction and easy access to, what is perceived as a low risk, entry level, potent narcotic. I would not expect that a PCA vial for a relative's cancer medicine would be terribly attractive to an adolescent. It requires a needle, it requires self-injection, it requires crossing a lot of thresholds all at one time.

On the other hand, a box of 24, 800 or 1600 mic *Actiq*™ might be viewed as an adolescent as a not terribly risky way to find out what opioids are like. And I suspect it might be riskier than they know. So

part of the risk management plan, part of the strategy, part of the process of responsibly marketing a product like this, is to think about how you minimize the unwholesome interactions that this product will have with the population, while optimizing the wholesome ones.

We had a patient here today describe how they thought out how to keep a barrier between their grandchildren and their medication. And I thought that was a pretty good plan. But that's -- have I got it right, Laura? Is that what you're talking about?

DR. McNICHOLAS: You've got it there.

CHAIRMAN DOWNS: I'm not sure which order, but I think -- why don't we just start and go this way. That would be the easiest thing for me. Dr. Max.

DR. MAX: A different issue which is the first statement on the label. It says, in the proposed label, ***Actiq***™ is indicated for patients already receiving and who are tolerant to opioid therapy. I wonder what a clinician is going to make of that. I know pain researchers can't agree on what is tolerant and how to measure it, and my suggestion would be, you had a very nice definition of patients who were eligible in the clinical trials.

By saying 50 of a Duragesic or 60 a day of Morphine, and you could say for a week or you wouldn't, you know, you wouldn't have to say that. I think if you just define it operationally it will really be a much better safety barrier than this, which I think may keep some deserving patients from getting the drug and expose others to risk.

DR. SHOEMAKER: I think you bring up a good point about the problem with defining opioid tolerance, and I think that's a good suggestion as well, to take the entry level criteria of 50 micrograms per hour was the minimum dose of Duragesic, and again, 60 milligrams a day of Morphine or Morphine-equivalent.

DR. MAX: Again, that would be something that a physician should be able to override without getting in trouble.

DR. SHOEMAKER: I understand what you're saying, but it's more guidance, that someone that was on two Percocets.

CHAIRMAN DOWNS: Dr. Raghavan.

DR. RAGHAVAN: As someone who just really spends his life treating cancer, and I don't have any real experience with the issues that the Drug Abuse Advisory Committee are wrestling with, I'm having a

logic problem in what I'm hearing.

On the one hand I see that there are facts that relate -- that Dr. Foley enunciated that relate to the numbers of patients that die in pain, and the availability of a new product that, from what I've been hearing today, sounds like a useful product that will help to overcome a particular phenomenon of breakthrough pain.

Against that I'm hearing a series of theoretical considerations about another drug of potential abuse. I haven't heard that it is definitely a drug of abuse -- although I would expect it to be so -- and a whole series of theoretical considerations about protecting a group of people who might become drug addicts if they have access to that product.

And what makes me uneasy is hearing Dr. Wright saying, should we be redefining the paradigm? And he can only respond to what he hears here. So it's not a criticism of Dr. Wright. But he's saying, you guys are advising me, and are you telling me we should go back to square one and start to reinvent the wheel?

Now, we have innumerable, narcotic analgesics that are available by mouth. If little

Johnny wants to try his first dose of narcotics he can take MS Contin, he can take oral Morphine tablets, he can take Oxycodone, etc. And it seems to me that the current discussion is going off into Wonderland. And I just don't understand why it's doing that.

I came here to discuss a product in terms of its efficacy; whether it would be better than, as good as, worse than, more dangerous than, an established product. And now we seem to have moved laterally into a speculative discussion on abuse potential. As someone who treats cancer, I think it would be a disaster if this meeting decided to redefine narcotic indications on the basis of abuse potential.

And what Dr. Cleary said a few minutes ago I agree with completely. We're in a situation where we have to deal with reality. The reality is, the health care system in the United States cannot afford inpatient consultation for its cancer patients, a vast majority of cancer patients don't have access to pain units.

For those pain units that are in operation, we all know that they are, as our oncologists, part and parcel of the drug abuse system to some extent. There will be patients being treated in pain center, in hospices, whose drugs will be diverted.

And so all of these theoretical considerations I think, are taking us away from our original theme, which is to try to evaluate the indices that I cited initially. I think it's reasonable to look at abuse potential at a later time, but I think the discussion for the last half hour has gone off into the realms of imagination and speculation.

CHAIRMAN DOWNS: Dr. de Wit.

DR. de WIT: I agree with the previous commentary completely and I feel like my comment is kind of going back to a more detailed aspect of what we were talking about. But we don't want to lose sight of the enormous benefits of this kind of product in light of the potential risks. I mean, we want to evaluate them but we don't want to overemphasize the risks.

I just wanted to make the point that, when we talk about the risks for the non-abusers, we know from laboratory studies that healthy volunteers without a history of drug abuse in general, don't like the effects of opiates anyway, although there might be some experimental use by family members or people who have the drug available.

Actually, these drugs have a very low risk

for being used repeatedly in a non-using population. So I don't think we should overemphasize that aspect of the risk. But I agree, we should regard this product in terms of the overall benefits and to not be too concerned about these possible risks.

I believe again, that the post-marketing surveillance will be an important element of this.

CHAIRMAN DOWNS: Dr. de Wit, I'd like to ask in response to what you just said, is that also true of Fentanyl? Because as an anesthesiologist, what we've heard is quite the opposite; that people in fact, do like the effect of Fentanyl and they like it very much, even on first exposure.

DR. de WIT: Generally, those people are self-selecting themselves. There are people, there are anesthesiologists or health professionals who already have a history of drug problems, and when even Fentanyl is administered to healthy volunteers, a small proportion -- maybe ten percent -- sometimes like the effects, and the large majority don't like the effects.

CHAIRMAN DOWNS: Because it's used as a pre-medicant in almost every single patient undergoing anesthesia, and it's used because it makes people feel good, I'm told by my residents.

DR. de WIT: I think it makes them feel good because it removes their pain, not because it makes them feel euphoriant.

CHAIRMAN DOWNS: No, not as a pre-medicant; that's not the case.

DR. de WIT: Well, I can refer you to the studies. We have evaluated people --

CHAIRMAN DOWNS: That why I say, as an anesthesiologist it seemed -- the impression is different. There may be studies showing that, but a lot of it is used for that reason.

DR. de WIT: In a clinical setting it might be different than in a laboratory, experimental setting.

CHAIRMAN DOWNS: Okay. Dr. Strain.

DR. STRAIN: Thank you. Dr. Strain from Baltimore. In response to some of the previous comments, I don't mean for us to become so obsessed with abuse liability that we lose sight of the potential clinical efficacy and importance of this product and all those points that are well recognized.

As I've thought about this product I think -- at times it becomes problematic in considering what could be going on in Wonderland because of the different populations that you're considering. So

that at times we're talking about what could happen with children who might get it and like it as a lollipop, what might happen with adolescents who want to explore and try it, and what could happen in the drug abuse population who are already opiate-dependent.

And I think, without belaboring this, it's simply that there isn't data here to help us in guiding that, and that might help us with things like the labeling of the product, to know, to be able to have said something about that.

In response to Dr. Wright's comments earlier, I don't think I'm necessarily advocating that things that are being indicated for schedule II have to have an abuse liability assessment, categorically. But I'm saying that it may be useful in the guidance of understanding the relative risk of using it -- a compound like this or something else that might come along, to be able to comment about it.

You might find that it's got a much lower abuse potential then IV Fentanyl, and that would be valuable to know as well.

CHAIRMAN DOWNS: Yes sir?

DR. BIGELOW: George Bigelow. I would just like to comment as someone who has been concerned with

assessment and reduction of abuse liability risk. It's well known that excessive concerns about abuse liability have dramatically restricted appropriate treatment of pain in this country.

And I think it would be a tragedy if excessive concern about potential abuse liability of this particular dosage form were to lead to greater restrictions that make the product unavailable to patients. We propose that the product be made available under the most restrictive conditions that the regulations allow.

Secondarily, I think it's a mistake to characterize us as going into this in an absence of data. Systematic abuse liability assessments of Fentanyl were published in 1965. Subsequent studies have been done in more recent years. I don't think we need to have abuse liability assessments with every new dosage form of a well-known medication in order to understand where it falls on the abuse liability continuum, and how we can appropriately regulate it.

I think this is a dosage form that as you suggest, may well have lower abuse liability than other dosage forms. At the same time, I think there's no question that doses in the 400 to 800 microgram range are going to produce euphoric effects in

populations who are experienced with opioids and seeking them out.

This seems to me that it provides us the information we need to proceed with making available under appropriate regulations, a safe and effective medication for a tragically undertreated pain condition.

CHAIRMAN DOWNS: Ms. Brown.

MS. BROWN: I'm Suzanne Brown from Portland, Oregon, and I have the privilege to live in this State. But last year we passed an assisted suicide law which has not actually gone into effect. It's been held up in the courts. But the biggest reason that law passed was due to undertreatment of cancer pain and/or the reality or fear thereof.

So I don't think we need to forget that and lose sight of it. We have patients who will die by their own hand and at their own choice because they feel like they can't get pain relief. So I do think we need to make sure we stay on a little bit of that focus while we have concern about the other.

But I would like to bring it back to another point of concern that I have, that I believe Dr. Rothstein actually mentioned earlier and that is, what about the 4-year-old to 8-year-old child who is now

proficient with scissors, can pick them up and open these packages, happens to get into a package of 1600 grams and sucks on it?

That's a concern I have. I tried to open the package earlier. I think that younger than 4-year-olds are going to have trouble getting in there, but I'm a little bit concerned about that group. I don't know. Is there something else that we can do to discourage that age group from using this? Is there such a possibly as a Mr. Yuk? I don't know anything about, you know, the trademarks here involved with that.

Is there a different -- can the outer packaging be more sturdy so at least they can't get into there as well? By that I mean the box that it's in. That's a pretty flimsy box. It wouldn't take a 3-year-old two minutes to open that.

That's a question I have for the sponsor. Have that looked at -- that age group really concerns me, because they might well be at risk here.

MS. ARNOLD: My name is Martha Arnold. I'm in the Marketing group at Anesta. There's a couple of comments I would like to make on the packaging and why it has been designed the way that it is.

As we've heard, *Actiq*™ provides some very

unique benefits. It's a very unique dosage form and as a result of that it needs unique packaging. It's from both a child-resistant perspective as well as from a stability perspective. I'd like to go back and correct a comment that was made earlier about the safety issues related to twist-off cap and whether or not that might be better.

We're trying to get that data. I don't have it available right now. But I can tell you that a twist-off cap package will not allow us to make this product available from a stability perspective. That is why it is in the pouch. And I think that that's an important point that needs to be made.

This package has been tested among the standard protocol that is currently available, which is that protocol that you heard described this morning which goes up to the age of approximately 51 months. The reason for this protocol, it is the same protocol as I understand it, that all of the manufacturers are required to meet. That is the only validated protocol that is available. And the study that you saw with the 99 percent effectiveness level in these children was conducted according that protocol.

To more directly address your question, ma'am, as it relates to the older-aged child, it's my

understanding that the reason that these are the same regs which all companies need to be involved with -- including those companies that make pleasant tasting products for children such as cold medicines and such as fever and pain relievers -- is that the expectation is that once a child reaches the 5- or 6-year-old age group, that he is capable of understanding the instructions of not attempting to get into the package.

That is the best point that I can make to you at this point in time. I can just share with you that that is our understanding of the situation and I'm not quite sure what else I can say that this point.

CHAIRMAN DOWNS: Yes, Dr. Palmer.

DR. PALMER: Overall -- this is Dr. Palmer from Colorado. I don't think it's fair to expect this committee to answer some of the global questions that have been put to it. And it's not that I'm blaming anyone for asking the questions; I'd like to have the answers to them to. I just -- I think it's not realistic for us to try to make a decision based on no data.

The health care system has changed so rapidly and the ethics that doctors are strugglin g

with in trying to take care of their painful patients are also changing so rapidly that it's very difficult to keep pace.

And I know the FDA and committees like this one were criticized this morning on CNN because of the weight reduction medications and the ineffectiveness of the warnings that were so carefully placed on these drugs; that they were not for frivolous or trivial weight reduction; that they were to be restricted to use of people who were significantly overweight or even morbidly obese.

And instead, as we all know now, they were used frequently and doctors were pushed very hard by lots of patients to give them these medications when they wanted only a trivial amount of weight loss.

We cannot prevent some of the diversion or some of the inappropriate use of this drug, but maybe as Dr. Wright brings up, it is time for a change in the way the FDA or this committee looks at drugs and agrees to relook at drugs.

And this is a perfect example of, what we'd love to do is give you permission to make this drug and use the plans that you have in place, but we would like to have a required re-examination with the data is available a year or two years from now, to see

where the drug is being diverted, how it is being used improperly.

Or maybe some novel uses have popped up that are totally appropriate, and whether or not poisonings and tragic deaths have actually occurred. Then we might be in some sort of a position to make recommendations about plugging up those holes or making safety considerations that make some sense.

I really think that part of the problem is this historical problem. Being a schedule II drug used to be fine and it used to be that those drugs were only used in hospitals. Well, guess what? You know, a decade ago is not today.

And one of our testifiers this morning who said that she's a nurse not allowed to inject spinal narcotics, and yet her patients are being taught to do this at home. I mean, what could be a better illustration of, here we thought it's something too dangerous for a registered nurse to do, we're now expecting some of our patients to do -- to give pain relief.

So in the face of this whirlwind change -- and hopefully a lot of it's a good change in terms of adequately treating pain patients -- I just don't think this committee can say that we know whether or

not there's a risk/benefit rat io that's positive, but we can say based on the best information we have, it looks like this product should be useful but w e require a relook at this sometime in the future.

And then either the committee meets again o r the FDA officials meet and re-evaluate this stuff, bu t we make that a requirement for approval of the drug.

CHAIRMAN DOWNS: Dr. Carlisle.

DR. CARLISLE: Sue Carlisle, U CSF. Just to expand your thoughts a little bit, I'd like to go bac k to the discussion that Dr. Wright brought up earlier about whether or not this drug should be restricted t o use only with cancer patients. It's my experienc e that, coming from an institution that has a large AID S population as well as a chronic pain clinic, that it' s obvious that these are going to be other indications for use for this drug.

The question that I have for the sponsor is , is there any thought of expanding the educationa l program to those settings?

DR. SHOEMAKER: I think the situation of th e HIV population would be a popu lation that we would go into next. Because if you think about it, it's very similar to cancer in that your life expectancy i s limited, there's a lot of pain, there's a lot o f

undertreatment of pain. And so I think that would be the next logical step -- that population in particular.

DR. CARLISLE: And chronic pain?

DR. SHOEMAKER: I think chronic pain would come next. I mean, as was pointed out by Dr. Farrar and Dr. Portenoy, that sometimes can be a controversial area. I think in the initial launch of this product it's appropriate to go to those physicians with a lot of experience, and I think the cancer pain physicians fit into that. I think a lot of the AIDS physicians also fit into that category. And I just think that chronic pain of non-cancer origin would be somewhere farther down the list.

CHAIRMAN DOWNS: Dr. Foley.

DR. FOLEY: I agree with the last two speakers on the issues that they raised, but another issue that relates to all of this is this issue of accountability for treating patient's pain. And if we're going to overemphasize the misuse of these drugs, could we somehow or other ask the FDA to put some weight behind the appropriate use of these drugs, and being assured that physicians are educated about pain and accountable for it?

Because that is really what the issue is,

and that would be at the heart of the matter. And not trying, again, to emphasize the negative aspects of these drugs, but rather the positive aspects.

CHAIRMAN DOWNS: Any other questions?

MS. CURLL: I'm back to the same comment. I find that this drug would be very, very beneficial to the population with pain and cancer. However, I still feel that your studies, after looking at the numbers -- and we talk about AIDS and we talk about breast cancer, and disproportionately HIV is in the Black and the Hispanic population -- again, the women with breast cancer that are Black and Hispanics are underserved. And looking at your numbers, you're very disproportionate, and I'm wondering if this cost factor will also have an impact on this population that you did not study.

CHAIRMAN DOWNS: Would the sponsor like to respond, or -- Dr. Wright?

DR. WRIGHT: I'd like the sponsor, who almost certainly has done some marketing studies, to respond by giving us a feel for -- let me ask this as a question. Is it the sponsor's opinion that this product provides a speed of analgesia and an extent of analgesia that is most similar to a PCA bolus or a parenteral narcotic?

And the second question -- part of that question is, what is the cost to a patient of at-home PCA? Do any of our people in the room know that?

DR. HEDEN: John Heden; I'm the business director for Abbott Pain Management, and I can speak to the cost of PCA therapy at home. Generally those pumps are distributed by home health care agencies. Those pumps can run -- and the services provided -- at around $3,000 a month for that type of therapy, which will be substantially higher than what we see *Actiq*™ being provided for in the marketplace.

DR. SHOEMAKER: If I could respond to another question you asked, Curtis, about the speed of onset. I think in our study we showed that the onset was similar to IV Morphine with the limitations that Dr. Portenoy raised about assay sensitivity. But I don't think we could say that it would be similar to the onset, for example, of IV Fentanyl, given the fact that Fentanyl is so much more lipid-soluble, more rapidly gets to the effect site in the brain.

So I think when we talk about parenterals, we specifically compared it to IV Morphine again, with the caveats that Dr. Portenoy pointed out.

DR. STANSKY: Don Stansky from Stanford. One of the panel members raised the issue of ethnicity

and gender, and from my understanding of Fentanyl clinical pharmacology, there's no reason to expect that -- there is no gender effect in terms of men versus women and Fentanyl kinetics.

And the studies that I've been involved in there's no evidence that there's any race effect in the basic disposition of the drug. And in terms of analgesic response, again, there's no -- there's some evidence that Asian races may have different analgesic responses to opioids, but beyond that there is no further evidence that other races respond differently to muagonists.

So I'm not certain that there's going to be a good scientific basis to say that certain subpopulations would respond different clinically to this drug.

MS. CURLL: I think that ethnicity and race are two different things, sir. Ethnicity and race are two different -- have different meanings.

DR. CLEARY: Jim Cleary from University of Wisconsin. Many of these patients will actually be eligible for the hospice Medicare benefit; many of these cancer patients near the end of life. If they sign onto the hospice Medicare benefit the hospice agrees to pay for their medicines.

That is a critical factor in this, so therefore, many of the costs will be borne by the hospice itself, and therefore covered by the per diem. The hospice people I've spoken to about this product see it as being an advantage to having to send a nurse out on call in order to provide intravenous analgesia at that time. So this is a potential benefit for these patients.

DR. SHOEMAKER: Dr. Walsh.

DR. WALSH: Thank you. Declan Walsh, Cleveland Clinic. I just want to respond to an issue that was raised about the cost of PCA versus oral medication. Because this is a very significant issue in the cost structure for the delivery of effective pain management in cancer patients.

Data from our own group which is not yet published, would suggest that for equivalent doses of Morphine delivered by PCA compared to oral administration, taking into account the oral parenteral ratio, for delivery of Morphine by PCA you're talking about roughly a 20-fold difference in the charges that are levied for the delivery of PCA in that setting. And that's obtaining the most favorable costs using a high volume provider and so on.

So I think that the issue, the central issue

here is, we have a huge problem of cancer pain management first of all, in society. Secondly, within the cancer pain population we have a huge problem with incident pain and breakthrough pain.

And currently, the only way to effectively manage that pain -- for example, in the thousands of patients who died of prostate cancer and have severe pain from metastasis every year -- the only way to effectively manage that pain in many of these patients is to use a PCA pump, which is considerably more complex, expensive, and so on.

We have here a unique product which offers a significant advantage in my view, in this very specific population. And I think that we should not let the conversation here about this product and about the management of this huge number of patients every year, be driven by the issues of abuse and so on -- although those need to be carefully considered.

But we have a unique product here which meets a very specific need, for which there's a huge requirement within this patient population. Thank you.

CHAIRMAN DOWNS: Dr. Watcha.

DR. WATCHA: Watcha; Dallas. I don't believe it's the role of this committee to discuss the

costs or relative costs of various approaches for it. I think our charge here is: is this drug safe, is this drug effective? And on that basis, what are the dangers of introducing this drug? I think the costs are interesting and appropriate for discussions, but not in this forum.

CHAIRMAN DOWNS: Dr. McCormick?

DR. McCORMICK: That is true, and I think perhaps with that in mind, I would like to ask if we could perhaps bring this discussion home to where we were early this morning and consider that this is a real dilemma for the FDA. There's no question that this is an area where there's a great need, and I think we've heard eloquently from a number of people, both on the committee and from the public, about this need, and no one denies that.

The dilemma that we face -- and as we've thought about this in looking at the sponsor's risk management plan and thinking about our own attitudes about the risk of this product -- is that there's a significant risk that we haven't even discussed yet really, in a significant way, and that is the risk to the child.

We like to think about, you know, what happens in the home situation? What happens when the

product has been partially used and set down? What happens when a child with a scissors gets a hold of this product and opens it up and there's a box of 96 of them?

I don't think that this is an all-or-none kind of discussion that we should be having. I think what we should be doing is looking for a compromise here. What can we do to minimize the risk to the child who stands to gain nothing from this product?

CHAIRMAN DOWNS: Would you like to respond to that?

DR. MAX: Sure. I think that one could always take the foil packet and put it inside a childproof container, but I think that may be overdoing it. I think, you know, with our kids when they were two years old, every cabinet was locked with all the cleaning fluids, and by the time kids get to be five or six years old the locks come off, they know that they're not supposed to get near something.

And I think any family where there's a cancer patient with a medicine should be able to instruct the kid. And I think one doesn't want to raise very costly, extra barriers. You know, you might find, if you find that 100 kids have overdoses you may have to insist on later change of the

packaging. But I think the plan thus far presented by the sponsor is reasonable.

DR. PATT: May I say something?

CHAIRMAN DOWNS: Yes, please.

DR. PATT: Richard Patt, M.D. Anderson Cancer Center in Houston. This discussion really forced me recently to think about how I talk to my patients about how they manage their medications in their home. And I think that this may be an opportunity to raise the standard for everybody.

For Abbott and Anesta, with this product where there's some perception of perhaps an increased risk, to perhaps raise the standard for all strong drugs in the home by enhancing physician's recognition of the risk this represents.

And so it may be a much broader benefit if we can really nail it down, because it's a terribly important issue and I realize that I need to do a better job, not just with OTFC but with immediate release Morphine Sulfate and other products. And I think this is a chance, again, to widen the circle a bit. It may be something very good that not just the companies, but the FDA can do to make the home safer. Thank you.

CHAIRMAN DOWNS: Were you saying then, that

you agree that this is a very significant risk in the home with children and so on, and that we haven't addressed it adequately in the past?

DR. PATT: I think of any medication in the home, and I think that it has been addressed. I'm clear from working with the sponsors, that they will -- they understand how important it is that physicians be educated in discussing this with their patients when they give them a prescription.

So I'm clear that this is a concern, a legitimate concern, that there's a plan to deal with it, and in fact, it may do a greater good than just for this product. Am I clear?

CHAIRMAN DOWNS: Yes. Does the sponsor have another response?

MS. KEDZIERA: Pam Kedziera from Fox Chase Cancer Center. As a nurse, what I do is educate patients about pain -- every day, on the phone, in person. I've helped NCI come up with a brochure and I've had to develop in our own center, specific sheets about pain medicines because they're not there. Because the only way I can be sure they get them is if I hand it to them.

This company has done something no other company with oral products has done. They're putting

a patient information sheet in every box. And that's not out there with any bottle of pills. I can never be assured that my patients get something. They have looked at this with other nurses -- myself included.

They have asked us for input on, what is a patient-readable material? They have added drawings to help show patients. They have videos to help -- they are going to convert from the studies to help show patients how to use this.

And the other part about patients leaving partially exposed units. Just like Dr. Patt said, every time a nurse hears about this product I hear, boy we're going to have to work harder at this. We do teach patients and families; they do take good care of it. They're scared. My families come in with grandchildren, children -- they come in as units. They are very frightened of opioids anyway.

This product, because it even looks different, makes us even more frightened. And I think if anything, myself included, if I was hesitant or I forgot or if I was rushed, I might not tell somebody -- oh, by the way, make sure that doesn't get in your children's hands. This product -- it's is like warning signals jump out at you, and you will do it more often than we normally do.

I really do think the company has addressed this better than any other company that I'm working with, or any other product that I have to teach anybody about.

CHAIRMAN DOWNS: Before I ask others to speak, I'd like to reiterate something that I said earlier which I'm still a little bit uneasy with. And that's, if we were discussing the use of this drug only with cancer patients, I would have personally, very little concern about its control, its efficacy, and so on.

But my concern still remains, what proportion of the market will be the cancer patient and what proportion will be this other group of patients -- the AIDS patients to begin with, and then the other chronic pain patients that we see in our clinic -- which usually are not cancer patients, usually are not AIDS patients -- those are a very specialized group going to the cancer hospital and to the AIDS unit of Tampa General Hospital.

But we have a very large pain clinic, many patients on narcotics, and I have grave concerns about those people and their responsibility to manage the drug, and I haven't heard that addressed at all, except that Dr. Wright earlier said, that in the past

the FDA has never required any further concern, other than the cancer patient -- that's a model for study.

But we've discussed many things other than studying the drug here today, and I'm still concerned about that.

Dr. Wright first, and then if appropriate, the sponsor can respond.

DR. WRIGHT: What I actually tried to say, and I hope I said it properly, is that it is only -- we have not required demonstration of efficacy in other chronic pain models, but we have put comments in with respect to safety. Where it appears that the migration of a product out of the intended population of use has raised a safety concern based on post-marketing data.

I am hearing a little bit from the Chair, and I think a little bit from the oncology people, that there may be different patterns of behavior in the cancer pain patient and some other chronic pain populations. I continue to listen with considerable interest.

DR. SHOEMAKER: Can we have a comment from Dr. Portenoy on this issue?

CHAIRMAN DOWNS: Yes.

DR. PORTENOY: I just would like to speak to

this issue of opioids for chronic, non-malignant pain. I think what the growing experience in this area is beginning to teach clinicians is that there is a subpopulation of patients in chronic, non-malignant pain who act for all the world like cancer patients.

This is what's driven the consensus statements of the American Pain Society and the American Academy of Pain Medicine, to recognize that this is appropriate therapy for a subpopulation of patients with chronic, non-malignant pain who handle these drugs in a responsible way for a long period of time, don't demonstrate any aberrant drug-related behavior, and act all the world like the modal cancer patient.

The patients who are referred to pain clinics are disproportionately represented by subtypes of patients who have problems with drugs, and this has been shown by five independent studies which have independently evaluated the populations referred to pain clinics as compared to chronic pain populations who live in the community.

So the perception that you may have from looking at a pain clinic population of patients with a relatively high prevalence of aberrant drug-related behavior, may come because you're looking at a pain

clinic population.

Nobody's advocating that everybody with chronic, non-malignant pain be treated with opioids, but the committee should recognize that there is a growing acknowledgment that there is a population of patients with pain due to osteoarthritis, osteoporosis, inflammatory conditions like rheumatoid arthritis, inflammatory bowel disease, hemophilia, as well as some medical diseases like Parkinson's disease and HIV disease; where there is significant undertreatment of pain.

And these populations -- there's a, again, a proportion of these patients who probably would benefit a great deal from greater access to opioid drugs by skilled physicians who don't have a stigmatized view of these drugs, and recognize that the patients who are coming to the office are not the same as the modal patient who's ending up in the pain clinic, in part because they were referred there for drug-taking problems.

I would really hope to allay your concerns about that. I think there's no question that this drug can be misused by a patient who is going to demonstrate aberrant drug-related behavior. But just like the substance abuse population that was discussed

before, the evidence at this point is that that represents a subgroup of chronic pain patients -- not all chronic pain patients -- and the fact that they exist, in my view, doesn't balance out the potential benefits of having this drug out there.

And I would just finish again, by this issue of balance. I think that we're always trying to weigh risk and benefit when we're trying to decide to make drugs available that will treat patients, and I think that the issue that you hear from the people who treat cancer and from myself -- who, I think has a view of non-cancer-related pain and the use of opioids, that is maybe more liberal than many physicians -- but what you hear out here is that it would be a mistake to lose sight of the importance of this balance.

The question is whether or not the availability of a potentially useful drug with an accessibility so that it can be used in the home to treat cancer patients as the primary targeted population, outweighs the more theoretical risk that a substance abusing population can use this drug, or as you're saying, a subgroup of chronic pain patients who have aberrant drug-related behaviors -- whether they would misuse it.

And I think you hear the tension in the room. I fall on this side; clearly a feeling that the access should be there, the drug should be released, and it should be done without the kinds of restrictions that are going to withhold it from the cancer population, because in considering the balance it falls on the side of those undertreated patients.

CHAIRMAN DOWNS: Now, don't misinterpret what I was saying. What I was saying is it's clear it would be efficacious in the patients with cancer pain. I don't think anyone has spoken to limiting access to those patients that I've heard today.

The question is the other patients -- and I've heard nothing about limiting its use in those patients either today, nor have I heard any mention of efficacy in those patients other than it potentially would be efficacious in those patients as well.

Yes sir. Dr. Rothstein.

DR. ROTHSTEIN: Dr. Rothstein. Does the sponsor have any information in the targeted populations, what percentage of those patients are having home visits by visiting nurse, whatever, and what your plans are for bringing that group into your education process?

When we used to do follow-ups for poisoning

in kids we'd get a visiting nurse into the home to go through the house and point out and help the family deal with lapses. If you've got a population of nurses that are going into the home they can help perhaps, in avoiding some of the problems that people talked about.

CHAIRMAN DOWNS: Dr. Callan.

DR. CALLAN: I'm Clair Callan. Just to remind you, or to emphasize that this morning when I was presenting the risk management program, yes, the home care nurses are included in our educational approach. They are a very important part of the caregiving that these patients need, and they will be fully educated onto the use and the control needed in this drug.

DR. PATT: I wonder if I can address the concern that you had about chronic, non-malignant pain because I don't have the figures at hand, but I suspect if you looked you'd find that drugs like transdermal Fentanyl which has an indication for pain that's sufficiently severe to require a strong opioid, probably 20 or 30 percent of it is used in non-cancer pain populations.

And I'm not aware of any studies that were brought to the FDA prior to its approval for a broad

indication.

I just want to make this distinction. I'm concerned that we're clear about what the sponsor's plan is in terms of education and marketing, because my understanding is that there's a marketing plan directed at this key population and key prescribers that take care of this population, but that education will be much more broad; that education will include both people that will probably use it -- like internists and family practitioners, the non-experts to keep them out of trouble -- but also people that shouldn't use it, like oral surgeons and acute pain physicians.

As a clinician I'm satisfied from the cancer pain work, or the work really with opioid tolerant patients or opioid exposed patients, that while there aren't specific outcomes in patients with non-cancer pain -- there are a few straggelers in these studies I think, that were cancer survivors and had cancer-related pain that was due to their treatment. They may have had chest wall pain after a thoracotomy.

But I would agree with Dr. Portenoy that the application of this is warranted based on the work that's been done so far. But I think lots of people need to be educated providers, even if they are not

the ones that are marketed to.

CHAIRMAN DOWNS: There was someone else at the microphone for the sponsor.

DR. WEINSTEIN: Thank you. Dr. Weinstein from M.D. Anderson Cancer Center. Perhaps there's one other point that you might find reassuring Mr. Chairman, and that is, when we do clinical analgesic trials in cancer pain, not all of our patients have cancer.

And what I mean by that is, not all of the patients that are studied, particularly in the long-term, open-label extension trials, have active disease. And they have many times, neuropathic pain as was just mentioned by Dr. Patt, as a result of their treatments.

And so as a subset of the clinical population being studied, those patients might be considered to be more like chronic, non-malignant pain patients than they are like active cancer patients. And so perhaps some of the long-term, open-label studies could be viewed from that perspective.

CHAIRMAN DOWNS: Dr. Strain.

DR. STRAIN: Eric Strain from Baltimore. A point and then a question. The point is that the label says it can be used for chronic pain. So

whatever happens, if that's th e approved label it can be used for chronic pain.

And if as a committee, we decide something different such as changing the recommendation of the label, then the committee can follow that route s o that it's chronic, you know, pain related pain relate d to a cancer. But whatever the label says is what can be done out there.

Let me shift gears and try to get back t o Dr. McCormick's point because she made an effort t o get us on a different tract and then we managed t o stray off. And I've thought a bout this question with respect to children quite a bit, having young childre n myself.

Monday nights in our household is cand y night where the kids can have candy after dinner. An d my daughter who's just turned four, can open any cand y package that has been manufactured in the world, and she can do it with scissors, her teeth, her hands . She's quite good at it. So this has worried me a s well.

And it led me to wonder about the use o f this on a stick -- this product. Because it woul d seem that making a coughdrop-like formulation migh t work better because then you could instruct th e

patient that if they are finished with it but there is still some solid product there, simply to swallow it. And you can't do that so long as you've got a stick.

And the problem with the stick is, if there's still something on it you've got to go off, run it under warm water -- and especially if they're getting sleepy from it which is one of the side effects -- you know, the dilemma is, it gets put down, somebody toddles in and picks it up.

So I'm sure the sponsor has worked through this and thought about the benefits and costs associated with a non-stick formulation, but I wonder if you could walk us through that, perhaps?

DR. SHOEMAKER: I think there's other features of the handle which must be considered as well and that is, that if a patient is having exaggerated effect as you mentioned, sleepy, they can remove it. That's important.

Another thing that was pointed out this morning is that if you swallow the Fentanyl you're not going to get a peak effect, and I think you might have a greater tendency to do that without the handle.

I think from a child safety point of view as well, is if you came across a child with an open bottle of MS Contin -- which by the way as Dr. Foley

pointed out, looks very much like candy -- you wouldn't know how many tablets the child had taken. Plus if the child chewed the MS Contin, they would be in a lot more trouble because it would lose it's sustained release properties.

So at least with the handle if unfortunately a child got into this -- and it would be a problem just as it would be with MS Contin -- at least you could recognize, wait a minute. This handle with the R_x, that's something wrong. And at least you would have the handle there to know exactly what the person got into.

And again, if you think about it, if you got into one package of *Actiq*™ you'd have one unit, and if you got into one bottle of pills, there potentially is a lot more analgesic there. And a statement was made but I don't think we should assume that a twist-off cap is necessarily more childproof. Again, in this study, I mean the efficacy of keeping children out was 99 person.

And so I don't think we can assume that children can get into *Actiq*™ any easier than they can into a twist-off bottle. Now that isn't to say there's not risk but again, it's relative risk and we have to look at things that are already there.

CHAIRMAN DOWNS: We'll have one more comment or question before we go to the open public hearing. Dr. Foley.

DR. FOLEY: I think we need to also remember that accidents are accidents. And I think to help Dr. McCormick, I think this whole discussion has been enormously useful to me to this issue of heightened awareness. And I think I'd ask the company to identify children in the home. We need to know how many cancer patients out there or how many patients that are receiving this drug do in fact, have children in the home.

And then in that setting, that's a group that will be targeted even more carefully with some kind of an educational program. So you just heighten it up, and it means that a message goes to the VNS and it goes to everyone that there are children in the home, be careful of drugs. And somehow or other, labeling that in a very, very positive way.

And I think those of us who are trying to educate the public, I think we should be adding to that message -- and this clearly -- you know, recent experience as I said, a child who overdosed on a parent's medication, and potentially intentionally, a 9-year old -- I think it sent a chilling effect

through us and it heightened our awareness, it made us talk to the VNS so differently, deal with everyone differently, and I think you're doing this Russ, and it's very helpful.

So I think we need to find out how many kids are out there in the population that are being exposed to this, what are the potential risks, study that, so that we can assure the public that it's safe, and we can learn the best ways to do it. I think education is the way. I think warning is as much heightened awareness. Constantly saying to the parents, where are the drugs? Have you put them in a separate place? Are they put away? And in some instances, if the house is so erratic or dysfunctional, considering that patients use a lockbox.

CHAIRMAN DOWNS: I'd like to go now to the open public hearing, and then we will resume the committee discussion following that. According to my agenda, Mr. Carl Dixon should speak. Is that correct? Is Mr. Dixon here? Are there any other comments during the open public hearing?

Well, seeing none, hearing none, what I would propose is that we take a short break now for 15 minutes and then resume at 3:30.

(Whereupon, the foregoing matter went off

the record at 3:12 p.m. and went back on the record at 3:35 p.m.)

CHAIRMAN DOWNS: I'd like to resume the meeting. It's my understanding that Mr. Dixon has arrived and so I would like to give him the opportunity of speaking during the Open Public Hearing. We'll reopen that. Mr. Dixon.

Mr. Dixon, you weren't here earlier. If you would please disclose any financial connection you have with Anesta or Abbott as well.

MR. DIXON: Yes, happily we have none. Or unhappily. I apologize for being late but United Airlines and Metro conspired.

Good afternoon. My name is Carl Dixon and I am the Executive Director of the National Kidney Cancer Association. I am here this afternoon to urge your approval of new drug application 20-747. This drug would be used in the management of chronic pain, particularly breakthrough pain in patients who already are receiving and who are tolerant of opioid therapy.

The National Kidney Cancer Association is based in Evanston, Illinois. We have active patient chapters in 19 major metropolitan areas across the nation. We are the only patient advocacy group for the 78,000 kidney cancer patients. We have

approximately 5,000 individual and family members.

The Association is governed by a Board of Directors composed of kidney cancer patients, surviving spouses and children. The Association has a Medical Advisory Board consisting of physicians and researchers who are among the world's foremost experts in renal and transitional cell carcinoma.

The Association was founded in 1990 by a group of patients and the National Volunteer President is Dr. Eugene P. Shoenfeld. The Association has not received any funds from Anesta and the cost of my travel here today is being paid for by the Association and not reimbursed by Anesta.

It is well known that millions of cancer patients experience acute and unnecessary pain because doctors undertreat their disease. At times this is due to unfounded concerns about the use of narcotics and strong pain relievers. Recently, the Agency for Health Care Policy and Research issued new pain treatment guidelines which call for early and aggressive treatment of pain. These guidelines also call for the use of the least invasive pain relievers possible such as oral medications, of which the drug presently before this panel is an excellent example.

In a survey conducted by the University of

Wisconsin and recently reported in The New York Times, 67 percent of the cancer patients surveyed suffered pain in the week prior to the interview. Of those who suffered that pain, 42 percent reported that they did not receive adequate pain therapy.

This problem is particularly concentrated among women, African-Americans, and Hispanics, as well as the elderly. The undertreatment of cancer pain needlessly increases the suffering of all cancer patients. In many cases it becomes so debilitating that it prevents patients from functioning in a normal manner.

In the population of kidney cancer patients that we serve, it is not unusual for individuals to develop metastatic disease to the spine or other bony areas. Many of these patients suffer breakthrough pain, by which I mean an intense flare of pain. Breakthrough pain occurs and it can be of moderate to severe intensity. It occurs in situations where controlled or persistent pain is being treated.

Presently, there is a severe shortage of approved medications for breakthrough pain, and it is estimated that as many as 800,000 Americans suffer every year from breakthrough pain.

I've previously discussed the major, public

health problem of unrelieved cancer pain. The very fact that there is such a problem highlights the need for new products to address cancer pain. If present products were adequate we would not see numbers like those reported in the University of Wisconsin study in The New York Times, nor would I receive telephone calls and E-mail messages on a regular basis from patients and caregivers who, in many cases, are frantic about pain.

There's a special need for new products to serve patient populations requiring such things as a rapid outset of therapy, non-invasiveness, convenience and low-tech treatments, and cost effectiveness. In the brave, new world of managed health care, patients get less professional hospital care and more assisted home care, or in many instances they are left to rely on self-care.

The need for simple, effective pain medication is changed by these changes to our health care system. One of the hardest things for cancer patients is losing control. Many of them will go to extraordinary lengths to avoid losing control. Often they do not report their pain to their physicians because they do not want to be considered as difficult patients. They often suffer because they do not have

a means to control their pain at home.

When pain breakthrough occurs, patients need to get immediate relief. They need to be able to get that relief whether they are at home or elsewhere. Many of them continue to try to lead normal lives, go to their offices to conduct their business while fighting cancer.

Invasive methods such as injection or infusion provide immediate relief but cannot be managed at home or elsewhere. Currently available short-acting, analgesics tablets, capsules, and elixirs, do not provide the prompt relief that these patients need. What is urgently needed is a non-invasive, rapid, pain relief agent.

I wish to thank the panel for allowing me to speak today on behalf of the 78,000 kidney cancer patients. I urge you to approve this application. This drug would provide an alternative to suffering breakthrough pain. It would enable cancer patients to be in control of their lives and lead more normal and rewarding lives as they continue their battle against cancer. Thank you.

CHAIRMAN DOWNS: Thank you, Mr. Dixon. We'll proceed back then to the panel discussion, and eventually what we'd like to do is lead to an

individual discussion. We'll go around the panel for the voting members and ask them to vote on the question that was given to us by the FDA.

But before we do that, however, I believe there's some questions from Dr. McCormick.

DR. McCORMICK: Again, to try to bring back our focus to the most vulnerable population that we haven't I don't feel, have fully discussed, and that is the pediatric population at risk.

Perhaps it would be helpful if the sponsor could address with the committee, what sorts of means you used during the clinical trail to ascertain how much of the product was used completely, how many residual units were left around, how you monitored for that? That might give us some idea of what the magnitude of the problem might be at homes.

DR. SHOEMAKER: Mike, could you help answer that question about potentially partially-consumed units -- how this was measured and how it was monitored in the clinical trials?

MR. BUSCH: Yes, Mike Busch, Anesta. During the clinical trials, as all clinical trials with all drugs, there's strict accountability of experimental materials, and in this case, whenever a patient consumed a unit they were required to bring back the

stick and the envelop that it was in. So there was complete accountability of that.

Most of the pharmacists that were part of the trials frowned upon returning partially-used Fentanyl on the stick, so we encouraged the patients to dispose of it in the way that we've instructed -- wash it under hot water. But we did ask the patients to -- and the study coordinators -- to record whether or not at least 90 percent of the units were consumed, so we knew when they were full consumptions.

DR. McCORMICK: And what were the results? I mean, what --

MR. BUSCH: There was virtually complete accountability. Just very rarely was there a stick not brought back. And the patients were coached quite a bit, both by the study coordinators, by the investigators, and also by videos that we produced, that they take the complete units. It was the only way we could really know what kind of data we were analyzing.

DR. McCORMICK: I guess what I'm driving at is, not whether people took the effort to wash off the sticks and bring back the sticks, but how many units were not completely consumed? I guess what I'm looking for is some sense of how much of a problem

this might be potentially, at home, where patients who are somnolent, not feeling well, may not be able to take the effort to dispose of the units adequately. How many of them may not --

MR. BUSCH: Don't have the numbers on the top of my head, but the vast majority of units were completely consumed.

DR. SHOEMAKER: Mike, I think we have some data that -- for in the controlled trials of 38,000 units there were only 151 that were not completely consumed. So that's the data in the short-term controlled trials combined.

And I think it's important to point out that one of the reasons that we have six dosage strengths is so that we can really encourage, and we do encourage, complete consumption of these units.

CHAIRMAN DOWNS: Any other questions, Dr. McCormick? Dr. Wright, did you have questions?

DR. WRIGHT: Much of my question has been pre-empted by Dr. McCormick. We are the FDA after all, and our empowering legislation was due in no small part, to public revulsion, that pediatric poisoning in the sulfonamide elixir episode.

We've heard a lot from the committee members today that it would not -- that one should not

inappropriately weigh the risk of accidental poisoning or of diversion and abuse in the balance with treating patients who need analgesia.

It would make no more sense to withhold drugs because they have risk associated with them, than it would be to say the children shouldn't travel in cars because they might get in an accident. But in cars we provide a car seat and we have legislation suggesting that you have to put your child in a car seat in many states.

And my question earlier in my presentation was, had adequate means been taken to reduce the risk of accidental injury? We've talked a lot about abuse, but I'd like to hear, as Dr. McCormick, some discussion of the adequacy of the strategies to prevent -- to reduce the number of units that are accessible to children to a minimum. And to minimize the risks that a child with a pair of scissors is going to intersect with a box of this product. That's the concern.

DR. SHOEMAKER: Well, I think one strong message that's come across very clear and that is, that in addition to child resistant packaging and so on, that we need to make a large effort at education. And I can't say how important we feel that is. And I

think we've heard that from the committee.

And again, this includes multiple ways to do this. You know, patient package inserts, the potential to have videos in the physician office, really making an effort with the oncology nurses and the visiting home health care nurses, and the clinicians themselves.

And I think that's something that we can say we're strongly committed to; trying to promote education, not only around this product -- and then hopefully there'd be a carryover to other products. So I think that's something that maybe wasn't emphasized in our initial program that perhaps does require more emphasis.

CHAIRMAN DOWNS: Dr. Wright, you look dissatisfied or puzzled. Did you want some response from the panelists as well?

DR. WRIGHT: Well, eventually we hope that we'll have a response from the panelists as to whether they think the plan is adequate, but during the breaks I hear members of the panel and a variety of people thinking and trying to grapple with this issue, but I just was listening to a sort of a silence and I was hoping that some of the members of the panel would speak up.

CHAIRMAN DOWNS: Well, what I'd like for the panel to now consider is the question which would respond to that. And that is: does the expected benefit to the intended clinical population outweigh the risk of accidental injury inherent in this product? So with that in mind I'd like to open it to the panel. Dr. de Wit.

DR. de WIT: I was wondering, what are the consequences of a child consuming -- say they consumed the full dose which means they'd have to use this product for 15 minutes. For say your lowest dose condition, what would be the health consequences? Toxicity? Okay, well a hypothetical child, 35 kilograms --

DR. SHOEMAKER: I think the consequences if a child got into a 1600 microgram unit -- and I guess the worst case scenario though, is that they don't just chew it and swallow it, because again, we know the peak level would be lower -- they would have to consume it over 15 minutes moving it around as we instruct patients, and so on and so forth.

I think the consequences could be life-threatening and quite similar to, if a child got into an MS Contin tablet and chewed up and swallowed a tablet. So yes, there is a definite risk there and

again, it's a risk that we have with other drugs and it's something -- it's why we're having this discussion. It's the reason that we need to put these safeguards in.

CHAIRMAN DOWNS: Somebody else had their hand up down there. Dr. Raghavan's reaching for the microphone.

DR. RAGHAVAN: Yes, Raghavan, Los Angeles. It seems to me that the thing that's bothering Dr. McCormick the most is the fact that this medication looks like a lollipop. It's by no means the only medication that's sweet -- Advil's sweet. There are a whole bunch of things that are out there that are sweet. But it's the fact that you can watch Grandma with or without cancer, sucking a lollipop and come back later on and think, hmm, tastes good, and then accidently get an overdose.

So the key issue as I see it relates not so much to the efficacy, which looks to me like it has activity, but what additional steps can be taken to prevent little Johnny from doing that.

And so perhaps what would be helpful would be if the company were able to develop, not only a package insert which probably 90 percent of patients and 50 percent of doctors won't read anyway, but

something on the box, something on the container that actually has a picture of a kid and a lollipop -- this is not my field -- but something that's easy and visual that makes patients remember how easy it would be for a kid to misunderstand that this is not candy and that it is dangerous.

We have cars, we have digoxin, we have a whole bunch of different things that present potential health hazards for our kids, but we don't regulate them because of theoretical concerns. What we do is, we put in the seatbelt. Sometimes you actually have to have the product out there. I mean, cars were there for a long time before seatbelts were developed.

And I think there's a limit to what Big Brother and the FDA can do to protect kids against imagined hazards. I do think that the concept of a very clear, visual message that comes on every packet, might be helpful in terms of warning patients that children are at risk.

CHAIRMAN DOWNS: Dr. Watcha.

DR. WATCHA: Another comment, Steve. You've had lots of experience with OTFC and kids, even under direct vision. When they get too drowsy with it, does it just slip out of the mouth?

DR. SHOEMAKER: Well again, I was describing

the worst-case scenario and you do bring up a point; that is, a child becomes sedated. There is always that potential for the unit to fall out of the mouth, which again is one of the advantages of the handle.

In which case we would expect peak blood level would be achieved in about five minutes later and then would start would start to rapidly fall. But again, I think we were trying to consider actually, the worst-case scenario.

And to take to a point that Dr. Raghavan was mentioning, on every pouch when you open every single unit, there's a warning and a box, and it may need to be worded a little bit differently than it is today, and we can test that. So every time you open a unit you should see this warning, hopefully, that will warn about appropriate use.

In addition, on the large box that 24 units come in, on the back of that box is a place where the pharmacist can put, you know, the person's name, take one of these every so often. And right there when you're reading those instructions, we would also like to have the warning, in addition to having them in a patient package insert.

So what we're doing then is looking for redundancy, trying to find those areas that will send

this message every time the patient hopefully, uses the product -- again, to talk about the safe and appropriate use and appropriate disposal, and what can happen to children, and so on.

CHAIRMAN DOWNS: Dr. Max.

DR. MAX: I think this product is one of the two or three most important innovations in cancer pain treatment in the past 40 years in terms of the impact it's going to have on large numbers of patients.

It appears to me that the company has thought carefully about the technology available to protect children, as it's also going to be one of the most profitable innovations and it's at risk. If anything happens, if many kids get poisoned, their market and their product is at risk. I want this to be available for a broad population of patients and that will be lost if they have a lot of accidents.

I think the market is going to really push them to be really scrupulous and go after every event that occurs in kids, and I don't think we can predict exactly what they're going to be. I think as long as the FDA -- if they report to the FDA and have a discussion every three months or six months or whatever you think is appropriate, I think they'll find out what they need to do, and I'm quite

comfortable.

CHAIRMAN DOWNS: Ms. Brown.

MS. BROWN: Well, I think the company has made a very reasonable attempt at that. We had a discussion during the break with them about the possibility of putting a Mr. Yuk thing on the end of the Orajet. They could then be broken off so that patients who wanted to use it in say a restaurant setting, were not necessarily stigmatized, but that -- well I mean, come on. Who wants to be sucking on a Mr. Yuk?

But then on the other hand, that way once a package is opened with a pair of scissors, it's much more visible. I don't think that the current whit e handle with nothing on it is really as visible as it ought to be. I think that's maybe an improvement that they can look at, but I certainly agree that I think it needs -- the product needs to be out there.

I do think the 4- to 8-year-old age group is an age group I'd like to see a little more concern shown to. I think they did a good job in the under 4 -- the 51 months and under -- 4-years-and-under group, in taking a look at that. But I think that's a minor modification that they can do that might help.

Nothing is going to prevent every accident.

Some kid, somewhere, somehow, sometime is going to do this. But do we deny everybody else -- and the answer I don't think is -- no, we don't.

CHAIRMAN DOWNS: Dr. McNicholas.

DR. McNICHOLAS: Just a couple of comments. First of all, I think that the idea expressed by Dr. Raghavan is great -- of having some kind of an icon-type thing that a child -- and a bar through it or something. Because I was just looking at the package that they handed him, and I can tell you, most people may read it the first time; they're not going to read that after that. So maybe something a little more obvious and picturesque or whatever, would be helpful.

The other thing -- I just heard something from the company that I hadn't heard before, and that's that they had a video. Is the video going to be available for the physician to show every patient on safe handling?

DR. SHOEMAKER: I think -- that is something that we're exploring right now. As someone pointed out, in the clinical trials we found the use of videos very effective in training patients how to use the product, how to totally consume the unit, and of course, in the clinical trials we also needed them to fill out diaries and so on.

So it's something that we're definitely considering. John Heden?

DR. HEDEN: Steve, I can add a little more detail, that yes, there will be a patient instruction video in the instruction and educational materials that are sent to the prescribing physicians. That is part of our marketing program.

CHAIRMAN DOWNS: What I'd like to do now is -- because we have a couple of panelists that must leave and the FDA has requested that the voting committee members make some comments and then vote yes or not -- I'd like to ask first Dr. Palmer to comment if she has any, and then answer the question whether or not you feel that the expected benefit in the intended clinical population outweighs the risk of accidental injury inherent in this project. And then for each of the panelists to consider that question. Dr. Palmer.

DR. PALMER: Thanks, John. I really think we need to think about what the required re-examination of the experience that you have once this product goes out. And I hope that that can be a positive experience, both for you and for us.

In fact, as I was telling Dr. Callan, that maybe you guys could set a highwater mark for how

dangerous drugs should be followed up when they're first issued and what kind of hazards they present.

You might want to even consider doing something like an immediate investigation if a poisoning does occur, so that you can gather as much information as possible from the first few really serious incidents. So that we 'll learn something and maybe can take appropriate steps with your product and any others that come out that are similar.

I would be interested in hearing back from you, or whoever sits in my place on this committee I'm sure would be in a year or two, to find out what the hazard is and how the drug is being used. And so I really expect you to collect that data and present it, but the other idea of maybe really actively and immediately investigating the first reports of toxicity might be something you want to consider.

In your education I wanted to comment; I think you're on the right track. Don't forget to educate the partners of the patients. And as I also suggested, Dr. Callan, you might to consider some kind of a program for retrieving the drugs that are in the home when your cancer patient dies. Some kind of perhaps, partial refund for product or some way of encouraging people to bring these back.

I wish that the people making Vicoden and the other drugs were doing something like this because right now there really is no incentive to either locate or properly dispose of these drugs.

In general, my answer to the question is that I believe that some efficacy for this drug has been shown. I am convinced by the testimony and by the basic research that this drug should have a good effect on breakthrough pain. I don't know what the risk is. I think everything that could be reasonably considered has been, and so I expect that the risk is reasonable.

So my answer to the question then, Dr. Downs, is that I believe the drug should be approved for distribution with careful instructions about how it's going to be followed up.

CHAIRMAN DOWNS: Thank you. Dr. Carlisle?

DR. CARLISLE: Sue Carlisle, UCSF. I also believe that we have shown a significant benefit in our deliberations today. I would again, like to urge the sponsor to extend the educational efforts to those uses that we might now consider off-label, because I think they're going to be used whether we think about it now or not.

Also, I think the idea of putting the visual

-- you know, a kid with a bar across it or something -- on the package is not a bad idea. Accutane has a pregnant woman with a bar across it on every pill, so it's not an unreasonable expectation to have.

CHAIRMAN DOWNS: Thank you. I'd like to begin then, with Dr. de Wit, to follow suit and we'll just go around the table, then. Any commentary and then your answer to the question.

DR. de WIT: My answer to the question is in agreement with the others speakers in the affirmative. I think we should vote for approval of the product with the proviso that they provide quantitative and timely post-marketing information that should be agreed on with the FDA at the time of approval.

CHAIRMAN DOWNS: Dr. Raghavan?

DR. RAGHAVAN: Yes, I agree with that and have nothing to add.

CHAIRMAN DOWNS: Dr. McNicholas?

DR. McNICHOLAS: I also agree that it should be approved but I would like to see some more work on the risk management plan in agreement with the FDA.

CHAIRMAN DOWNS: Just to make it clear, the question that we're really answering is, does the expected benefit outweigh the risk, and not to approve the drug, particularly. The FDA will do that of

course, but --

DR. McNICHOLAS: Right. But I do think that it's --

CHAIRMAN DOWNS: And I assume the answer is Still the same?

DR. McNICHOLAS: Yes, that the expected benefit does outweigh, but I would like to see some more work on the risk management.

CHAIRMAN DOWNS: Dr. Hertz?

DR. HERTZ: I think that this is probably a very good breakthrough for cancer pain. I think the drug will be a very good drug. I do think that there are some issues that have been raised here which are a question and which have to be safeguarded.

Perhaps the company can set up an 800-number where physicians and other practitioners can call up and ask if they have any questions, and can report any problems that develop with the drug immediately so that people can act and we don't have to wait a week or a month.

Parke-Davis has done this with Neurantin as an off-label pain product rather than a seizure drug. But I think the drug should be -- the benefits of the drug outweigh the risks at this time.

CHAIRMAN DOWNS: Dr. Max?

DR. MAX: I agree that the benefits greatly outweigh the risks. A few small points about the labeling. As I mentioned before, I think the language that it should only be used in tolerant patients should be changed to be much more operationally defining the patient's narcotic dose.

And there are also some things in the present proposed labeling like the comparison of the *Actiq*™ onset with the prior rescue dose which is, I think, an unfair comparison. It's unblinded, it's using only the successful patients. Even though it claims the *Actiq*™ works faster, the placebo *Actiq*™ also worked faster. So I think that should -- I think only the good data, and there's plenty of it, should be in the brochure.

CHAIRMAN DOWNS: Dr. Rothstein?

DR. ROTHSTEIN: Dr. Rothstein. I think the benefits outweigh the undefined risk, unmeasurable at this time, and would push for voluntary home visits to reinforce the safe use of this drug.

CHAIRMAN DOWNS: Ms. Brown?

MS. BROWN: Suzanne Brown. I definitely think that the benefits outweigh the risks. I think the company has done a reasonable job of looking at that. I think we've made suggestions for where they

might look elsewhere.

I also would make one other comment to the company; that when they have on their packaging, opioid-tolerant patients, I don't know that the general public understands that term and that they might look at that terminology and change it.

CHAIRMAN DOWNS: Dr. Rohde?

DR. ROHDE: Yes, Chuck Rohde from Johns Hopkins. I agree with the idea that the benefits clearly outweigh the risks. I believe that some of the answers to the questions that we've heard might exist in the data that are currently available.

CHAIRMAN DOWNS: Dr. Watcha?

DR. WATCHA: I agree with the previous speakers. I believe the benefits clearly outweigh the risks. As a pediatrician I have a philosophical problem of having a picture of a kid with a slash going through it. That might be appropriate for a birth control device, but perhaps we could use something else. Thank you.

CHAIRMAN DOWNS: I would certainly vote yes on this issue. I still would express the concern that the intended clinical population seems to be the patient with cancer pain here, and I have a feeling that that may not be the ultimate intended clinical

population. And if that was considered, then I would have a greater difficulty with the question.

But if we're just considering the cancer patient or the patient with AIDS now, I would certainly be in favor of it.

Dr. Horlocker?

DR. HORLOCKER: I also agree that the benefits outweigh the risks of this, however I would like to point out that only 257 chronic pain patients have been studied and I would like to see additional information on the frequency of somnolence and possible hypoventilation and hypercardia in these patients. It may be that perhaps 100 microgram beginning dose would be more appropriate.

CHAIRMAN DOWNS: But you would say yes in answer to the question now.

MS. CURLL: Mary Curll. Yes, I agree that the benefits do outweigh the risk in today's environment of managed care. I think your primary care physicians are going to be using this drug and you might want to make sure they get educated, too.

CHAIRMAN DOWNS: Dr. Lowenstein?

DR. LOWENSTEIN: At the risk of being boring, I also will agree that the benefits outweigh the risks. I think the discussion has been excellent

and the contributions of the palliative care physicians, the oncologists, and the pain medicine physicians I think have been extremely important in putting these issues into perspective.

I also will cast my vote that really very close follow-up is mandatory so that we do understand what problems we get into and can address them.

CHAIRMAN DOWNS: An unusually quiet Dr. Woods today.

DR. WOOD: Well, yes, I think Fentanyl is a drug whose pharmacology is very well recognized and what's new today are two things. One is the route of administration and secondly, that we're looking at the drug for a specific indication. And I think the sponsor has certainly shown efficacy as far as those two things are concerned.

And I think it's interesting that the risk, the adverse response has not centered on the patient, but is rather centered on different groups rather than the patient themselves.

I think pediatric poisoning is always going to be a problem. It exists for tricylates, for digoxin, for many other drugs. I think the important thing is to address the problem. I think the sponsors have taken initial measures that may have to be

changed somewhat in the future, but the only way we'll get data is by actually using the drug in different situations. And I feel that the benefits do outweigh the risks, and I also would vote for approval.

CHAIRMAN DOWNS: Dr. Ellis?

DR. ELLIS: John Ellis, Chicago. I agree that as presented, there is evidence of efficacy, and I would be happy with approval in the patients in whom efficacy has been shown, which for me are patients with malignancy and pain.

CHAIRMAN DOWNS: Dr. Savarese?

DR. SAVARESE: John Savarese, New York, Cornell. I agree with everybody else in that it's definitely a beneficial product and that our only concern is the risk involved of accessibility to inappropriate populations such as children.

I think that with proper monitoring and with proper publicity and education, that risk can be reduced, minimized. And all I wanted to add to this is that nobody yet has mentioned that there is a relatively safe antagonist to the narcotic effects of Fentanyl or any other opioid. And should we -- not today but at some point -- think about making the antidote accessible to families who have a family member who is using this kind of breakthrough

treatment.

CHAIRMAN DOWNS: Dr. Young?

DR. YOUNG: I'd have nothing to add to the discussion about the drug. I think that the benefits do outweigh the risks. In the hope however, that the package insert for the patients might be read by the people who are using the med, I would suggest that the type be made a little larger so it would be a little easier to read when it's finally manufactured.

CHAIRMAN DOWNS: Dr. Foley and Dr. Strain are non-voting I guess here. Do you have any final comments? Dr. McCormick, Dr. Wright, Dr. Kahn?

DR. WRIGHT: If the committee has no more suggestions or comments to make to us, and if the sponsor has no other comments, we may be done.

DR. McCORMICK: I just would like to thank you very much for your thoughtful consideration.

CHAIRMAN DOWNS: Thank you all very much. The meeting is adjourned.

(Whereupon, the Anesthetic and Life Support Drugs Advisory Committee was adjourned at 4:12 p.m.)